REMARKS

Reconsideration of this application is respectfully requested.

Status of the Claims

Claims 1-12 are pending in this application. Claims 7, 11, and 12 have been withdrawn as being directed to nonelected subject matter.

Claim 1 has been amended to recite "[a] method for treating an acute or chronic lesion or a degenerative disease of the nervous system by stimulating the polymerization and/or the stabilization of microtubules in a patient, comprising the administration to said patient, of an effective quantity of a drug comprising 3β-methoxy-pregna-5-ene-20-one (3-methoxy-PREG) or a molecule derived from pregnenolone that contains a 3-methoxy function and is incapable of being converted into a metabolite or ester sulfate of pregnenolone." Support for this amendment can be found in original claim 1 and in the specification at page 13, lines 5-9.

Dependent claims 2-6 and 8 have been amended to refer to the method of claim 1. Claims 2-6 and 8 have also been amended to replace the term "the aforementioned" with the term "said."

Claim 9 was amended to recite "[a] drug consisting of methoxy-PREG." Support for the amendment to claim 9 can be found in original claim 9.

No new matter has been introduced by the foregoing amendments.

Election/Restrictions

The Examiner required restriction to the following two groups of claims:

Group I Claims 1-10, drawn to a use of 3-methoxy-pregnenolone (3-methoxy-PREG) or a molecule derived from pregnenolone, and an excipient for the preparation of a drug to treat an acute lesion, a chronic lesion or a degenerative disease; and

Group II Claims 11-12, drawn to methods for increasing the stabilization and/or inducing the polymerization of microtubules, or neuritic sprouting comprising 3-methoxy-pregnenolone.

Applicant elects Group I, claims 1-10, drawn to a use of 3-methoxy-PREG or a molecule derived from pregnenolone, and an excipient for the preparation of a drug to treat an acute lesion, a chronic lesion, or a degenerative disease.

In addition, the Examiner required an election of species from each of the following three groups:

Group A An acute lesion, a chronic lesion, or degenerative disease, for the purpose of examining claim 1;

Group B Alzheimer's disease, Parkinson's disease, age-induced memory loss, a cerebral lesion, a lesion of the spinal cord, and the disease recited therein, for the purpose of examining claim 2; and

Group C 3-methoxy-PREG or a molecule derived from pregnenolone of formula (I), as recited therein in claim 1.

Applicant elects "an acute lesion from Group A, a "cerebral lesion" from Group B, and "3-methoxy-PREG" from Group C. Upon the allowance of a generic claim, Applicant requests the Office to consider claims to additional species, which include all the limitations of the allowed generic claim, in accordance with 37 C.F.R. § 1.141. Meanwhile, Applicant is retaining all of the claims for possible rejoinder during examination on the merits. Claims 1-6 and 8-10 are readable on the elected invention.

Objection to Claims

The Examiner objected to claims 4-8 as allegedly "being in improper form because a multiple dependent claim cannot depend from other multiple dependent claims." Office Action at 9.

In response, Applicant points out that amended claims 4-8 depend from only claim 1. As such, Applicant respectfully submits that claim 9 is in proper form.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-9 were rejected as being indefinite under 35 U.S.C. §112, second paragraph, for allegedly "failing to particularly point out and distinctly claim the subject matter which the Applicant regards as his invention." Office Action at 9.

The Office particularly rejected claims 1-8 because "it is unclear what method/process applicant is intending to encompass," with respect to the "use" of 3-methoxy-pregnenolone. Office Action at 9-10. The Office also applied the foregoing rationale to reject claims 1-8 under 35 U.S.C. §101, allegedly "because the claimed recitation of use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101." Office Action at 10.

In response, Applicant first points out that Claim 7 has been withdrawn from prosecution as not reading on the elected species. Thus, the rejection of claim 7 has been rendered moot.

With regards to claims 1-6 and 8, Applicant points out that, as amended, these claims do not recite the term "use" and instead recite "A method for treating an acute or

chronic lesion or a degenerative disease of the nervous system by stimulating the polymerization and/or the stabilization of microtubules in a patient, comprising the administration to said patient, of an effective quantity of a drug comprising 3β-methoxy-pregna-5-ene-20-one (3-methoxy-PREG) or a molecule derived from pregnenolone that contains a 3-methoxy function and is incapable of being converted into a metabolite or ester sulfate of pregnenolone, wherein said molecule derived from pregnenolone is of formula I." As such, Applicant respectfully submits that the Office's rationale for rejection has been obviated because the claims recite a method of treatment with at least the active steps of administering a drug to a patient and stimulating the polymerization of said patient's microtubules.

The Office also rejected claims 1-6 and 8 because it is allegedly unclear whether the recitation of the term "aforementioned" refers to a claim term recited by independent claim 1 or a claim term recited by each of the dependent claims 2-6 and 8, respectively. Office Action at 10.

In response, Applicant points out that amended claims 1-6 and 8 do not recite the term "the aforementioned," but instead recite the term "said," which unambiguously refers to claim terms in independent claim 1. Accordingly, Applicant respectfully submits that the Office's rationale for rejecting claims 1-6 and 8 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite has been obviated.

The Office also rejected claim 9 as being indefinite because allegedly, "it is unclear that the claim is directed to 3-methoxy-pregnenolone as a drug only or is directed to a composition comprising 3-methoxy-pregnenolone as a drug." Office Action

at 10. In response, Applicant points out that amended claim 9 recites "[a] drug consisting of 3-methoxy-PREG." Accordingly, the utilization of the closed language terminology "consisting of" in claim 9 unambiguously indicates that the drug is 3-methoxy-PREG. Thus, Applicant respectfully submits that the Office's rationale for rejecting claim 9 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite has been obviated.

Rejection under 35 U.S.C. §102(b)

Claims 1-6 and 8-10 were rejected as allegedly being anticipated by Chopp *et al.* (US 6,245,757). Office Action at 11. More specifically, the Office states that:

> With respect to claims 1-3, 6, 9 and 10, Chopp et al. disclose a use of a progestin, i.e. pregnenolone methyl ether . . . which facilitates rapid transport of a steroid to the brain, is effective in reducing infarct size following acute, focal ischemia, i.e. middle cerebral artery occlusion, when given before and after the onset of ischemia (column 3, line 63-67; column 4, line 1 and column 5, line 4). As a result, the ischemic tissues, including tissues of the central nervous system, can be treated so as to improve tissue survival and to hasten general bodily recovery (column 4, line 23-26).
>
> Chopp et al. also disclose that the progestin is administered to a mammal in combination with one or more pharmaceutical excipients (column 6, line 1-2). More specifically, Chopp et al. disclose that the progestin compound is formulated to pass through the blood-brain barrier and enters the central nervous system at widespread sites (column 12, example 2: line 9-11).

Office Action at 12-13. The Office relies on the foregoing interpretations of Chopp *et al.* to allege that claims 1-6 and 8-10 are anticipated because these claims allegedly "are directed to a process of preparing a pharmaceutical composition, in an injectable or an oral form, comprises [*sic*] 3-methoxy-pregnenolone . . . present in an amount of 50 to

2500 mg and an excipient." Office Action at 11. Applicant respectfully traverses for the following reasons.

The Cited Art Erroneously Classifies 3-methoxy-PREG as a Progestin

Applicant respectfully points out that Chopp *et al.* teaches the use of progestins, but not 3-methoxy-PREG, for treating brain lesions resulting from ischemia. More particularly, Chopp *et al.* states:

> It is believed that the present method functions, at least in part, by the ability of the progestin to reduce the damage caused by ischemia, i.e., the brain damage caused by cerebral ischemia, and its aftereffects. The efficacy of the present method may also be due to enhancement of the ability of the brain to recognize after damage, by enhancing its intrinsic ability to compensate for injury.

Chopp *et al.* at column 2, lines 38-45.

Applicant notes that Chopp *et al.* fail to disclose mechanisms by which progestin permits the reduction of brain damage caused by ischemia and for how progestin enhances the brain's ability to recognize and compensate for injury.

Furthermore, Applicant submits that the conclusions of Chopp *et al.* that relate to the effects of progestins were reached by generalizing experimental data obtained by using only progesterone, the natural hormone on which the families of progestin and progestagens are based. Indeed, the only data that are presented by Chopp *et al.* were derived from experiments that tested the effect of progesterone on brain lesions resulting from ischemia.

Applicant points out that the medical community defines a progestin as "a natural or synthetic progestational substance that mimics some or all of the actions of

progesterone." See the enclosed copy of the entry for the definition of "progestin" in *The Free Dictionary*. Thus, Applicant further submits that a progestin is a compound that has progesterone activity, i.e. an agonist of the progesterone receptor.

The fact that progestins possess progesterone activity is also confirmed by the reference by Chopp *et al.* to the "bioactive metabolites" of progesterone. *See* Chopp *et al.* at column 2, lines 50-51. Applicant submits that the term "bioactive metabolites" in reference to progesterone suggests that only metabolites of progesterone that retain progesterone activity are envisaged.

Chopp *et al.* also contains additional support for the notion that progestins should be understood as compounds that have progesterone activity, by its teaching that "effective amounts of progesterone or other progestins can be delivered . . . in order to mitigate or block the effects of stroke-induces ischemia." Chopp *et al.* at column 4, lines 9-12.

In view of the teachings of Chopp *et al.* that progestins should have progesterone activity, Applicant respectfully submits that any compound that is cited by Chopp *et al.*, which does not have progesterone activity, would not have been recognized as a progestin by an ordinarily skilled artisan at the time of the invention. Thus, Applicant submits that the classification of compounds, which do not have progesterone activity, as progestins would be erroneous. Indeed, although the mechanism of action of progestins for treating ischemia-induced brain lesions is not elucidated in Chopp *et al.*, Applicant submits that a person of ordinary skill in the art would have understood from the teaching in Chopp *et al.* that the mechanism of action involves progesterone activity.

The "Detailed Description of the Invention" section of Chopp *et al.* cites a long list of compounds that are presented as useful. This list includes progesterone and a list of compounds that includes well-known synthetic progestins, such as 5-dehydroprogesterone and megestrol acetate, as well as molecules corresponding to numbers 267-284[1] and 7908 to 7915 of the Merck Index, 12th edition (the Merck Index[2]). However, Applicant points out that no teaching was provided by either Chopp *et al.* or the Merck Index, which demonstrated that the listed compounds of the Merck Index have progesterone activity.

Moreover, Applicant submits that some of the cited compounds are not progestins, and thus, can not activate the progesterone receptor. For example, 5β-reduced steroids (3,20-pregnanedione), as well as pregnenolone methyl ether (or 3-methoxy-pregnenolone), are not progestins.

With particular regard to 3-methoxy-pregnenolone, Applicant submits that the absence of progesterone activity is first deducible from the enclosed review article by Bursi and Groen concerning structure-activity relationships of progestins, which are referred to therein as progestagens. Bursi and Groen, (2000) Eur. J. Med. Chem. 35:787-96. Applicant submits that Bursi and Groen formally exclude the possibility that a compound with the chemical structure of 3-methoxy-pregnenolone could have progesterone activity. Indeed, Bursi and Groen indicate that structure-activity

---

[1] Chopp *et al.* refer to molecules 266-286. However, the molecules referred to by name in Chopp *et al.* at column 4, lines 59-60, which include allopregnone-3-α. or 3-β, 20-α or 20-β-diol, appear to better correspond with molecules 267-284.

[2] Copies of relevant pages are enclosed.

relationship (SAR) studies showed that for there to be progesterone activity, "1) hydrogen bond accepting substituents at C-3 and C-17 [positions of the ligand] are required." *See* Bursi and Groen at 788, last paragraph.

However, Applicant submits that 3-methoxy-PREG is unable to form a hydrogen bond at the C-3 position because it has a methoxy at that position, and methoxy groups are unable to form hydrogen bonds. In addition, Applicant points out that the methoxy group at C-3 of 3-methoxy-pregnenolone is an ether group, and ethers are not capable of accepting a hydrogen bond. *See* the first sentence of the enclosed Wikipedia Article entitled *Physical Properties*. Thus, Applicant submits that in view of Bursi and Groen, one of ordinary skill in the art at the time of the invention would have known that compounds that were not capable of forming a hydrogen bond at the C-3 position could not have had progesterone activity. Accordingly, Applicant submits that one of ordinary skill in the art at the time of the invention would have excluded 3-methoxy-pregnenolone from progestins suitable for practicing the invention of Chopp *et al.*

Also, the absence of progesterone activity by 3-methoxy-pregnenolone is further demonstrated by the enclosed additional data submitted by Applicant. These data show that 3-methoxy-PREG is unable to activate a progesterone receptor activity reporter gene. Moreover, these data also show that 3-methoxy-PREG can act as a dose-dependent antagonist of the pregnenolone receptor. Thus, Applicant submits that these data support the teaching of Bursi and Groen, that 3-methoxy-PREG has no progesterone activity and that one of skill in the art at the time of the invention could not have looked to Chopp *et al.* for teachings that 3-methoxy-pregnenolone has

progesterone activity and that it could be used to treat ischemic damage by activating the same mechanism that is activated by progesterone, even though 3-methoxy-PREG is *erroneously* cited in Chopp *et al.* among a list that is mainly composed of true progestins. As such, Applicant submits that Chopp *et al.* failed to disclose teachings related to the use of 3-methoxy-pregnenolone to treat neuronal damage caused by ischemia.

Furthermore, Applicant submits that even if one of ordinary skill in the art had tested 3-methoxy-PREG for progesterone activity in spite of the teachings to the contrary of Bursi and Groen, the skilled artisan would have discovered that 3-methoxy-PREG would not have activated the progesterone receptor and thus, would not be effective for treating ischemic injury according to the treatment method taught by Chopp *et al.*, which does not address the 3-methoxy-PREG-mediated mechanism involving the stimulation of the polymerization or the stabilization of microtubules, or both. Accordingly, Applicant submits that claims 1-6 and 8-10 are not anticipated by Chopp *et al.*

The Cited Art Fails to Teach all the Elements of the Rejected Claims

Also, in order for cited art to anticipate a claimed invention, the M.P.E.P. requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131 (8th ed., 5th rev. 2007) (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

With the foregoing guidance from the M.P.E.P. in mind, Applicant submits that Chopp *et al.* does not teach all the elements of amended claim 1, the claim from which all other claims depend. For example, Chopp *et al.* fails to provide any teachings that relate to treating an acute or chronic lesion or a degenerative disease of the nervous system by stimulating the polymerization and/or stabilization of microtubules in a patient, as recited by the instant claims.

More specifically, Chopp *et al.* exemplifies only progesterone for the treatment of ischemic injury. However, Applicant points out that the instant specification teaches that progesterone does not stimulate the polymerization of microtubules and that it is an antagonist of the microtubule polymerization activity of pregnenolone, the precursor molecule of 3-methoxy-PREG and progesterone. See Specification at 4, lines 7-10; and at 16, lines 16-20. Thus, the mechanisms of action by which 3-methoxy-PREG and progesterone have beneficial effects on the brain following ischemic injury are different. Chopp *et al.* does not teach a method for treating an acute or chronic lesion or a degenerative disease of the nervous system by stimulating the polymerization and/or the stabilization of microtubules. Accordingly, Applicant submits that the Office can withdraw the rejection of claims 1-6 and 8-10, under 35 U.S.C. §102(b).

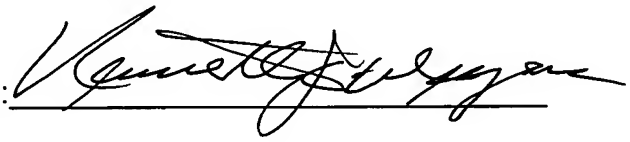
In view of the foregoing remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 22, 2008

By: 

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progestin

Also found in: Medical, Wikipedia, Hutchinson

0.06 sec.

pro·ges·tin (prō-jĕs'tĭn)

n.

1. A natural or synthetic progestational substance that mimics some or all of the actions of progesterone.
2. A crude hormone of the corpus luteum from which progesterone can be isolated in pure form. No longer in scientific use.

[pro-[1] + gest(ation) + -in.]

Thesaurus

Legend: Synonyms | Related Words | Antonyms

Noun 1. progestin - any of a group of steroid hormones that have the effect of progesterone

- progestogen
- sex hormone, steroid hormone, steroid - any hormone affecting the development and growth of sex organs
- Lipo-Lutin, progesterone - a steroid hormone (trade name Lipo-Lutin) produced in the ovary; prepares and maintains the uterus for pregnancy
- megestrol, megestrol acetate - a synthetic progestational compound used to treat endometrial carcinoma
- norethandrolone, norethindrone, norethindrone acetate, Norlutin - a synthetic progestational hormone (trade name Norlutin) used in oral contraceptives and to treat endometriosis
- norethynodrel - a progesterone derivative used in oral contraceptives and in the control of menstruation and the treatment of abnormal uterine bleeding
- norgestrel - synthetic progestin used in oral contraceptives
- medroxyprogesterone, Provera - a progestin compound (trade name Provera) used to treat menstrual disorders

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CHEMICALS, DRUGS, AND BIOLOGICALS

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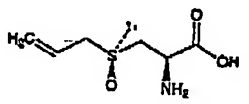
1996

Caution: A strong irritant. Can be absorbed through skin.

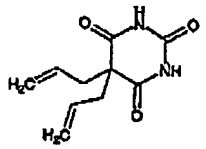
USE: Herbicide.

260. Alliin. *(S)-3-(2-Propenylsulfinyl)-L-alanine; 3-((S)-allylsulfinyl)-L-alanine; S*-allyl-L-cysteine sulfoxide. $C_6H_{11}NO_3S$; mol wt 177.22. C 40.66%, H 6.26%, N 7.90%, O 27.08%, S 18.09%. Constituent of garlic, *Allium sativum L., Liliaceae;* also found in other *Allium* spp. Isoln: Stoll, Seebeck, *Helv. Chim. Acta* 31, 189 (1948). Synthesis: *eidem, Experientia* 6, 330 (1950); *Helv. Chim. Acta* 34, 481 (1951).



Hemihydrate, odorless, bunched needles from dil acetone, mp 164-166° (effervescence). $[\alpha]_D^{25}$ +63.5° (c = 2). Freely sol in water. Practically insol in abs ethanol, chloroform, acetone, ether, benzene. Upon cleavage by the specific enzyme alliinase, an odor of garlic develops, and the fission products show antibacterial action similar to allicin, *q.v.*

261. Allobarbital. *5,5-Di-2-propenyl-2,4,6(1H,3H,5H)-pyrimidinetrione; 5,5-diallylbarbituric acid;* allobarbitone; Malilum; Diadol; Dial. $C_{10}H_{12}N_2O_3$; mol wt 208.22. C 57.69%, H 5.81%, N 13.45%, O 23.05%. Prepn: U.S. pat. 1,042,265 (1912). Acute toxicity: F. Sandberg, *Acta Physiol. Scand.* 24, 7 (1951).

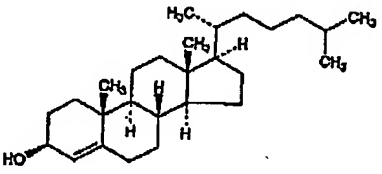


Crystals, leaflets. Slightly bitter taste, mp 171-173°. One part dissolves in about 300 parts water, 50 parts boiling water, 20 parts cold alcohol, 20 parts ether; very sol in hot alcohol and in acetone; sol in ethyl acetate. Insol in aliphatic hydrocarbons. A satd aq soln is acid to litmus. LD_{50} i.p. in rats: 127.3 mg/kg (Sandberg).

Caution: May be habit forming. This is a controlled substance (depressant) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.13 (1995).

THERAP CAT: Sedative, hypnotic.

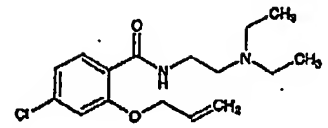
262. Allocholesterol. *(3β)-Cholest-4-en-3-ol;* coprostenol; 4:5-coprosten-3-ol. $C_{27}H_{46}O$; mol wt 386.66. C 83.87%, H 11.99%, O 4.14%. Prepn: Windaus, *Ann.* 459, 101 (1927); Schoenheimer, Evans, *J. Biol. Chem.* 114, 567 (1936). Sepn from cholesterol: Stoll, *Z. Physiol. Chem.* 246, 10 (1937).



Needles from ether-methanol, mp 132°. $[\alpha]_D^{25}$ +43.7° (c = 1 in benzene). Freely sol in benzene, acetone, ether, chloroform, dioxane, pyridine; less sol in methanol, alcohol. Pptd by digitonin. Deep-red color with 90% trichloroacetic acid.

Acetate, $C_{29}H_{48}O_2$, long needles from dil methanol, mp 85°.

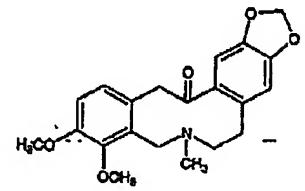
263. Alloclamide. *4-Chloro-N-[2-(diethylamino)ethyl]-2-(2-propenyloxy)benzamide; 2-(allyloxy)-4-chloro-N-[2-(diethylamino)ethyl]benzamide.* $C_{16}H_{23}ClN_2O_2$; mol wt 310.82. C 61.83%, H 7.46%, Cl 11.41%, N 9.01%, O 10.29%. Prepn: Mauvernay, U.S. pat. 3,160,557 (1964 to C.S.R.M.).



Hydrochloride, an ingredient of *Dégryp.* Crystals from abs alcohol + ether, mp 125-127°. Sol in abs alcohol. LD_{50} orally in mice: 740 mg/kg.

THERAP CAT: Antitussive, antihistaminic.

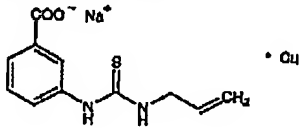
264. Allocryptopine. *5,7,8,15-Tetrahydro-3,4-dimethoxy-6-methylbenzo[g][1,3]dioxolo[4,5-k][3]benzazecin-14(6H)-one.* $C_{21}H_{23}NO_5$; mol wt 369.42. C 68.28%, H 6.28%, N 3.79%, O 21.65%. Isomeric with cryptopine, *q.v.* Obtained from *Chelidonium majus* L., *Bocconia cordata* Willd., *Sanguinaria canadensis* L. and allied *Papaveraceae:* Manske in Manske, Holmes, *The Alkaloids* vol. IV (Academic Press, New York, 1954) p 159. Structure: Gadamer, *Arch. Pharm.* 257, 298 (1919). Exists in two isomeric modifications designated as α- and β-forms. Identity of α-form with α-fagarine: Redemann *et al., J. Am. Chem. Soc.* 71, 1030 (1949). Synthesis: Haworth, Perkin, *J. Chem. Soc.* 1926, 445; Bentley, Murray, *ibid.* 1963, 2497.



α-Allocryptopine, *α-fagarine.* Crystals from ethanol, mp 160-161°. Soluble in alcohol, chloroform, ether, ethyl acetate and dil acids.

β-Allocryptopine, crystallizes with ½ mol of alcohol or ethyl acetate. Melts after expelling the solvent, at 169-171°.

265. Allocuprelde Sodium. *3-[[(2-Propenylamino)thioxomethyl]amino]benzoic acid monocopper (1+) monosodium salt; m-[(N-allyl-1-mercaptoformimidoyl)amino]benzoic acid copper derivative sodium salt;* 3-[1-(3-allyl-*S*-cupropseudothiourcido)]benzoic acid sodium salt; *m*-[[(allylimino)mercaptomethyl]amino]benzoic acid *S*-copper derivative sodium salt; sodium 3-(3-allyl-*S*-cuproisothiourcido)-benzoate; sodium 3-(3-allyl-*S*-cupropseudothiourcido)-benzoate; cuprothiosinamine *m*-benzoate sodium; cupralylnatrium; cupralylsodium; Cuprelon; Cupralene; Cuprion; Ebesal. $C_{11}H_{11}CuN_2NaO_2S$; mol wt 321.82. C 41.05%, H 3.45%, Cu 19.75%, N 8.70%, Na 7.14%, O 9.94%, S 9.96%. Prepd by heating *m*-aminobenzoic acid with allyl isothiocyanate and treating the resulting *m*,ω-allylthioureidobenzoic acid with cuprous chloride: Bockmühl, Fritzsche, Ger. pat. 551,421 (1932 to I. G. Farben).

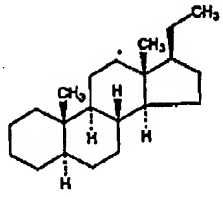


Dark brown powder. Freely sol in water. Insol in alcohol, ether.

THERAP CAT: Antirheumatic.

266. Allopregnane, *(5α)-Pregnane.* $C_{21}H_{36}$; mol wt 288.52. C 87.42%, H 12.58%. Prepn from corticosterone: Steiger, Reichstein, *Helv. Chim. Acta* 21, 161 (1938); from allopregnan-3-one: Ruzicka *et al., ibid.* 22, 1294 (1939); from 21-hydroxyallopregnane: Plattner *et al., ibid.* 27, 1177

(1944); Casanova, Reichstein, *Ibid.* 32, 647 (1949); by degradation of conessine: Haworth *et al.*, *J. Chem. Soc.* 1949, 831; by Hofmann decomposition of 3β- and 3α-dimethylaminopregnanes: Haworth *et al.*, *Ibid.* 1953, 1110.



Crystals from acetone + methanol, mp 84–85°. $[\alpha]_D^{19}$ +18.4° (c = 1.69 in chloroform).

267. Allopregnane-3α,20α-diol. *5α-Pregnane-3α,20α-diol;* 3α,20α-dihydroxy-5α-pregnane. $C_{21}H_{36}O_2$; mol wt 320.52. C 78.70%, H 11.32%, O 9.98%. Progesterone metabolite. Isoln from human pregnancy urine: Beall, *Biochem. J.* 31, 35 (1937); from bulls' urine: Marker *et al.*, *J. Am. Chem. Soc.* 60, 2931 (1938). Prepn by reduction of 5α-pregn-1-ene-3,20-dione with lithium aluminum hydride: Schütt, Tamm, *Helv. Chim. Acta* 41, 1751 (1958).

Crystals from methanol, mp 243–245°. $[\alpha]_D^{20}$ +17° (c = 0.148 in ethanol).

Diacetate, $C_{25}H_{40}O_4$, crystals, mp 139.5–140.5°. $[\alpha]_D^{20}$ +18° (c = 0.408 in benzene).

268. Allopregnane-3α,20β-diol. *(3α,5α,20R)-Pregnane-3,20-diol;* 3α,20β-dihydroxy-5α-pregnane. $C_{21}H_{36}O_2$; mol wt 320.52. C 78.70%, H 11.32%, O 9.98%. Progesterone metabolite. Prepn by hydrogenation of progesterone: Marker, Lawson, *J. Am. Chem. Soc.* 61, 588 (1939); by catalytic hydrogenation of epiallopregnane-3-ol-20-one: Marker, U.S. pat. 2,231,019 (1941 to Parke, Davis); by reduction of 5α-pregn-1-ene-3,20-dione with lithium aluminum hydride: Schütt, Tamm, *Helv. Chim. Acta* 41, 1751 (1958).

Needles from acetone, mp 207–209°. $[\alpha]_D^{25}$ +12° (c = 1.132 in chloroform).

269. Allopregnane-3β,20α-diol. *5α-Pregnane-3β,20α-diol;* 3β,20α-dihydroxy-5α-pregnane. $C_{21}H_{36}O_2$; mol wt 320.52. C 78.70%, H 11.32%, O 9.98%. Progesterone metabolite. Isoln from pregnant mares' urine: Brooks *et al.*, *Biochem. J.* 51, 694 (1952). Prepn by heating 3α,20α-dihydroxy-5α-pregnane with sodium, or by hydrogenation of 5α-pregnane-20-ol-3-one in acid: Marker, U.S. pats. 2,196,220 and 2,230,962 (1940, 1941, both to Parke, Davis); by reduction of allopregnan-3β-ol-20-one acetate with sodium: Klyne, Barton, *J. Am. Chem. Soc.* 71, 1500 (1949); by reduction of 5,16-pregnadien-3β-ol-20-one with Zn + acetic acid: Ercoli, De Ruggieri, *Farm. Sci. Tec. Pavia* 7, 11 (1952), *C.A.* 46, 10186b (1952).

Crystals from acetone, mp 218–219°. $[\alpha]_D^{22}$ +23° (c = 0.93 in chloroform).

Diacetate, $C_{25}H_{40}O_4$, crystals from petr ether, mp 164–165°. $[\alpha]_D^{19}$ +0.8° (c = 1.2 in chloroform).

Dibenzoate, $C_{35}H_{44}O_4$, crystals, mp 170.5–172°. $[\alpha]_D^{19}$ +27.7° (c = 0.84 in chloroform).

270. Allopregnane-3β,20β-diol. *(3β,5α,20R)-Pregnane-3,20-diol;* 3β,20β-dihydroxy-5α-pregnane. $C_{21}H_{36}O_2$; mol wt 320.52. C 78.70%, H 11.32%, O 9.98%. Progesterone metabolite. Isoln from pregnant mares' urine: Brooks *et al.*, *Biochem. J.* 51, 694 (1952). Prepn by catalytic reduction of allopregnane-3,20-dione: Marker *et al.*, Brit. pat. 512,940 (1939 to Parke, Davis); by hydrogenation of pregn-5-ene-3β-ol-20-one: Klyne, Barton, *J. Am. Chem. Soc.* 71, 1500 (1949); by hydrogenation of pregn-5-ene-3β,20β-diol: Klyne, Miller, *J. Chem. Soc.* 1950, 1972.

Leaflets from ethyl acetate + petr ether, mp 194.5–195.5°. $[\alpha]_D$ +4.4° (c = 1.04 in chloroform).

Diacetate, $C_{25}H_{40}O_4$, needles from ethyl acetate + petr ether, mp 141–142.5°. $[\alpha]_D^{20}$ +21° (c = 1 in chloroform).

Dibenzoate, $C_{35}H_{44}O_4$, crystals, mp 237.5–239°. $[\alpha]_D^{28}$ −10.1° (c = 2.08 in chloroform).

271. Allopregnane-3β,21-diol-11,20-dione. *3β,21-Dihydroxy-5α-pregnane-11,20-dione;* 3β,21-dihydroxy-11,20-dioxo-5α-pregnane; Kendall's compound H; Reichstein's substance N. $C_{21}H_{32}O_4$; mol wt 348.48. C 72.38%, H 9.26%, O 18.36%. Isoln from adrenal glands: Steiger, Reichstein, *Helv. Chim. Acta* 21, 546 (1938). Prepn by reduction of allopregnan-21-ol-3,11,20-trione acetate: Mancera *et al.*, *J. Am. Chem. Soc.* 77, 5669 (1955).

Hydrated crystals from dil acetone; anhydr shiny spears from benzene or acetone, mp 189–191°. $[\alpha]_D^{19}$ +93.8° (c = 1.4 in abs ethanol).

3,21-Diacetate. $C_{25}H_{36}O_6$, clusters of needles from ether-pentane, mp 148–149.5°. $[\alpha]_D^{18}$ +77.5° ± 2.5° (acetone); $[\alpha]_D^{18}$ +85.6 ± 2° (dioxane).

272. Allopregnane-3β,17α-diol-20-one. *3β,17-Dihydroxy-5α-pregnan-20-one;* 3β,17-dihydroxy-20-oxo-5α-pregnane; 17-(1-ketoethyl)androstane-3,17-diol; Reichstein's substance L; Wintersteiner's compound G. $C_{21}H_{34}O_3$; mol wt 334.50. C 75.41%, H 10.25%, O 14.35%. Isoln from adrenal cortex: Wintersteiner, Pfiffner, *J. Biol. Chem.* 116, 291 (1936). Structure: Reichstein, Gätzi, *Helv. Chim. Acta* 21, 1497 (1938). Prepn from allopregnan-3β-ol-20-one 3-acetate: Rosenkranz *et al.*, *J. Am. Chem. Soc.* 72, 4081 (1950); from pregn-5-ene-3β-ol-20-one: Ramirez, Stafie, *Ibid.* 77, 134 (1955).

Crystals from abs alcohol, mp 264–265°. $[\alpha]_D^{25}$ +30.6° (c = 0.54 in abs alcohol).

3-Acetate, $C_{23}H_{36}O_4$, crystals from acetone, mp 187–189°. $[\alpha]_D^{20}$ +18° (acetone).

273. 3,20-Allopregnanedione. *5α-Pregnane-3,20-dione;* 3,20-dioxo-5α-pregnane. $C_{21}H_{32}O_2$; mol wt 316.48. C 79.70%, H 10.19%, O 10.11%. From pregnancy urine: Lieber-Hartmann, Lacher, *Helv. Chim. Acta* 18, 160 (1935); Lieberman *et al.*, *J. Biol. Chem.* 172, 263 (1948). Prepn from pregna-4,11-diene-3,20-dione: Shoppee, Reichstein, *Helv. Chim. Acta* 24, 356 (1941); by oxidation of allopregnan-3β-ol-20-one with chromium trioxide: Billeter, Miescher, *Ibid.* 30, 1409 (1947); by hydrogenation of pregnenolone: Pappas, Nace, *J. Am. Chem. Soc.* 81, 4556 (1959); from funtumine: Janot *et al.*, *Bull. Soc. Chim. France* 1960, 1669.

Crystals from methylene chloride + hexane, mp 200°. $[\alpha]_D$ +125° (c = 1.2 in chloroform).

USE: In the synthesis of progesterone, Fr. pat. 845,034, *C.A.* 34, 8184[2] (1940).

274. Allopregnane-3β,11β,17α,20β,21-pentol. *5α-Pregnane-3β,11β,17,20β,21-pentol;* 3β,11β,17,20β,21-pentahydroxy-5α-pregnane; 17-(1,2-dihydroxyethyl)androstane-3,11,17-triol; Kendall's compound D; Reichstein's substance A; Wintersteiner's compound A. $C_{21}H_{36}O_5$; mol wt 368.51. C 68.45%, H 9.85%, O 21.71%. Occurs in adrenal cortex: Mason *et al.*, *J. Biol. Chem.* 114, 613 (1936). Prepn from 21-acetoxy-3β,17α-dihydroxy-5α-pregnane-11,20-dione + lithium aluminum hydride: Klyne, Ridley, *J. Chem. Soc.* 1956, 4825; by hydrogenation of cortisol with platinum oxide: Caspi, *J. Org. Chem.* 24, 669 (1959).

Crystals from methanol, mp 159–163°, resolidifies and mp 215–216°. $[\alpha]_D^{25}$ +9.8° (c = 0.56 in methanol).

275. Allopregnane-3β,17α,20β,21-tetrol. *Pregnane-3,17,20,21-tetrol;* 3β,17,20β,21-tetrahydroxy-5α-pregnane; 17-(1,2-dihydroxyethyl)androstane-3,17-diol; Reichstein's substance K. $C_{21}H_{36}O_4$; mol wt 352.51. C 71.55%, H 10.29%, O 18.13%. Isoln from adrenal cortex: Steiger, Reichstein, *Helv. Chim. Acta* 21, 546 (1938). Prepn by reduction of allopregn-17-ene-3,17-diol 3,21-diacetate with osmium tetroxide: Serini *et al.*, *Ber.* 72, 391 (1939).

Leaflets from dilute methanol, mp 198–200°. $[\alpha]_D^{25}$ −1.0° (c = 1 in abs ethanol).

3,20,21-Triacetate, $C_{27}H_{42}O_7$, rods from ether + pentane, mp 179°. $[\alpha]_D^{25}$ +53.2° (c = 1.9 in acetone).

276. Allopregnane-3α,11β,17α,21-tetrol-20-one. *3α,11β,17,21-Tetrahydroxy-5α-pregnan-20-one;* 3α,11β,17,21-tetrahydroxy-20-oxo-5α-pregnane; 17-(1-keto-2-hydroxyethyl)androstane-3,11,17-triol; 3α-allotetrahydrocortisol; Kendall's compound C; Reichstein's substance C; Wintersteiner's compound D. $C_{21}H_{34}O_5$; mol wt 366.50. C 68.82%, H 9.35%, O 21.83%. Isoln from adrenal cortex: Mason *et al.*,

J. Biol. Chem. 124, 459 (1938); Kuizenga, Cartland, *Endocrinology* 24, 526 (1939); v. Euw, Reichstein, *Helv. Chim. Acta* 25, 988 (1942); v. Euw *et al. ibid.* 41, 1516 (1958). Prepn by hydrogenation of cortisol with rhodium: Caspi, *J. Org. Chem.* 24, 669 (1959); from bismethylenedioxyhydrocortisone: Fukushima, Daum, *ibid.* 26, 520 (1961).
Crystals from methanol, mp 244-245°. $[\alpha]_D^{25}$ +59.7° (c = 0.34 in methanol).
3,21-Diacetate, $C_{25}H_{38}O_7$, crystals, dec 204-205°. $[\alpha]_D^{20}$ +73.8°; $[\alpha]_{546}^{20}$ +90.5° (dioxane).

277. Allopregnane-3β,11β,17α,21-tetrol-20-one. *3β,11β,17,21-Tetrahydroxy-5α-pregnan-20-one;* 3β,11β,17,21-tetrahydroxy-20-oxo-5α-pregnane; Reichstein's substance V. $C_{21}H_{34}O_5$; mol wt 366.50. C 68.82%, H 9.35%, O 21.83%. Isoln from adrenal cortex: von Euw, Reichstein, *Helv. Chim. Acta* 25, 988 (1942). Prepn from 5α-pregnan-3β-ol-11,20-dione: Chamberlin, Chemerda, *J. Am. Chem. Soc.* 77, 1221 (1955); by hydrogenation of cortisol with rhodium: Caspi, *J. Org. Chem.* 24, 669 (1959); from bismethylenedioxyhydrocortisone: Fukushima, Daum, *ibid.* 26, 520 (1961).
Needles from dilute methanol, decomp 220-225°. $[\alpha]_D^{25}$ +50.7° (c = 0.8672 in dioxane).
3,21-Diacetate, $C_{25}H_{38}O_7$, flat prisms from acetone-ether, decomp 225-227°. $[\alpha]_D^{25}$ +62.6° (c = 1.101 in dioxane).

278. Allopregnane-3β,17α,20α-triol. *5α-Pregnane-3β,17,20α-triol;* 3β,17,20α-trihydroxy-5α-pregnane; Reichstein's substance O. $C_{21}H_{36}O_3$; mol wt 336.52. C 74.95%, H 10.78%, O 14.26%. Isoln from adrenal glands: Steiger, Reichstein, *Helv. Chim. Acta* 21, 546 (1938). Prepn from allopregn-16-en-3β-ol-20-one: Plattner *et al., ibid.* 31, 2210 (1948); Julian *et al.,* U.S. pat. 2,662,904 (1953 to Glidden).
Leaflets from dil methanol, mp 222-223°. $[\alpha]_D^{20}$ −12.55° (c = 1.195 in methanol).
3,20-Diacetate, $C_{25}H_{40}O_5$, crystals by sublimation, mp 252°. $[\alpha]_D^{25}$ −30.1° (c = 1.097 in acetone).

279. Allopregnane-3β,17α,20β-triol. *5α-Pregnane-3β,17,20β-triol;* 3β,17,20β-trihydroxy-5α-pregnane; 17-(1-hydroxyethyl)androstane-3,17-diol; Reichstein's substance J. $C_{21}H_{36}O_3$; mol wt 336.52. C 74.95%, H 10.78%, O 14.26%. Isoln from adrenal cortex: Reichstein, *Helv. Chim. Acta* 19, 1126 (1936); Steiger, Reichstein, *ibid.* 21, 546 (1938). Prepn from 3β-acetoxy-16α,17α-oxido-20-oxo-5-allopregnane: Plattner *et al., ibid.* 31, 2210 (1948); Brit. pat. 665,254 (1952 to Ciba); from 3β-acetoxy-17α-hydroxyallopregnan-20-one: Fukushima, Meyer, *J. Org. Chem.* 23, 174 (1958).
Rhomboid needles from dil acetone, mp 216-217°. Sublimes in high vacuum. $[\alpha]_D^{18}$ −7.9° (c = 1.77 in abs alc).
3,20-Diacetate, $C_{25}H_{40}O_5$, crystals from pentane, mp 161-162°. $[\alpha]_D^{20}$ +24.6° (c = 2.11 in acetone).

280. Allopregnane-3β,17α,21-triol-11,20-dione. *3β,17,21-Trihydroxy-5α-pregnane-11,20-dione;* 3β,17,21-trihydroxy-11,20-dioxo-5α-pregnane; 17-(1-keto-2-hydroxyethyl)-androstane-3,17-diol-11-one; Kendall's compound G; Reichstein's substance D; Wintersteiner's compound B. $C_{21}H_{32}O_5$; mol wt 364.48. C 69.20%, H 8.85%, O 21.95%. Occurs in adrenal cortex: Kuizenga, Cartland, *Endocrinology* 24, 526 (1939); von Euw, Reichstein, *Helv. Chim. Acta* 25, 988 (1942); 41, 1516 (1958). Prepn by reduction of allopregnane-17α,21-diol-3,11,20-trione: Kaufmann, Pataki, *Experientia* 7, 260 (1951); from 5α-pregnan-3β-ol-11,20-dione: Chamberlin, Chemerda, *J. Am. Chem. Soc.* 77, 1221 (1955).
Crystals from abs alc, mp 238-242°. $[\alpha]_D^{20}$ +61.8° (c = 1.07 in dioxane).
3,21-Diacetate, $C_{25}H_{36}O_7$, crystals, mp 223-224°. $[\alpha]_D^{20}$ +72.3° (dioxane).

281. Allopregnane-3β,11β,21-triol-20-one. *3β,11β,21-Trihydroxy-5α-pregnan-20-one;* 3β,11β,21-trihydroxy-20-oxo-5α-pregnane; Reichstein's substance R. $C_{21}H_{34}O_4$; mol wt 350.50. C 71.96%, H 9.78%, O 18.26%. Isolation from adrenal glands: Reichstein, von Euw, *Helv. Chim. Acta* 21, 1197 (1938); Reichstein, *ibid.* 1490. Partial synthesis by hydrogenation of corticosterone acetate: Pataki *et al., J. Biol. Chem.* 195, 751 (1952). Prepn from 3β,11β-dihydroxy-alloetiocholanic acid: Lardon, Reichstein, *Helv. Chim. Acta* 37, 443 (1954); from hydrocortisone: Mancera *et al. J. Am. Chem. Soc.* 77, 5669 (1955); from 3β,21-diacetoxy-17(20)-allopregnene + osmium tetroxide and triethylamine oxide peroxide: Schneider, Hanze, U.S. pat. 2,769,823 (1956 to Upjohn).
Needles from alc, mp 202-204°. $[\alpha]_D$ +110° (ethanol).
3,21-Diacetate, $C_{25}H_{38}O_6$, crystals from acetone + ether, mp 170-172°. $[\alpha]_D^{21}$ +82.5° (c = 1.38 in dioxane); $[\alpha]_D^{18}$ +101° (acetone).

282. Allopregnane-3β,17α,21-triol-20-one. *3β,17,21-Trihydroxy-5α-pregnan-20-one;* 3α,17,21-trihydroxy-20-oxo-5α-pregnane; Reichstein's substance P. $C_{21}H_{34}O_4$; mol wt 350.50. C 71.96%, H 9.78%, O 18.26%. Isoln from adrenal glands: Steiger, Reichstein, *Helv. Chim. Acta* 21, 546 (1938); Reichstein, Gatzi, *ibid.* 1185. Partial synthesis from cholesterol: Reichstein, von Euw, *ibid.* 24, 401 (1941). Prepn from allopregnan-3β-ol-20-one: Rosenkranz *et al., J. Am. Chem. Soc.* 72, 4081 (1950); from 3β-acetoxy-21-bromo-17α-hydroxy-2-oxoallopregnane: Kaufmann *et al.,* U.S. pat. 2,596,562 (1952 to Syntex).
Pointed needles from abs ethanol, decomp 230-239°. $[\alpha]_D^{20}$ +48.0° (c = 0.938 in abs ethanol). Freely sol in alcohol, acetone. Sparingly sol in ether, water.
3,21-Diacetate, $C_{25}H_{38}O_6$, crystals from benzene, mp 208-210°. $[\alpha]_D^{20}$ +41.5° (chloroform).

283. Allopregnan-3α-ol-20-one. *3α-Hydroxy-5α-pregnan-20-one;* 3α-hydroxy-20-oxo-5α-pregnane; epiallopregnan-3-ol-20-one. $C_{21}H_{34}O_2$; mol wt 318.50. C 79.19%, H 10.76%, O 10.05%. Isoln from pregnancy urine of women: Marker *et al., J. Am. Chem. Soc.* 59, 616 (1937); Lieberman *et al., J. Biol. Chem.* 172, 263 (1948); Davis, Plotz, *Acta Endocrinol.* 21, 245 (1956). Prepn from pregnenolone: Fleischer *et al., J. Am. Chem. Soc.* 60, 79 (1938); Schwenk *et al.,* U.S. pat. 2,180,614 (1940 to Schering); by reduction of allopregnane-3,20-dione: Soloway *et al., J. Am. Chem. Soc.* 75, 2356 (1953).
Crystals from abs alc, mp 176-178°. $[\alpha]_D$ +87.7° (abs alc).
Acetate, $C_{23}H_{36}O_3$, crystals from aq ethanol, mp 141-142°. $[\alpha]_D^{22}$ +94.5° (abs ethanol).

284. Allopregnan-3β-ol-20-one. *3β-Hydroxy-5α-pregnan-20-one;* 3β-hydroxy-20-oxo-5α-pregnane. $C_{21}H_{34}O_2$; mol wt 318.50. C 79.19%, H 10.76%, O 10.05%. Isoln from adrenal cortex: von Euw, Reichstein, *Helv. Chim. Acta* 24, 885 (1941); from corpus luteum: Butenandt, Mamoli, *Ber.* 68, 1847 (1935); Prelog, Meister, *Helv. Chim. Acta* 32, 2435 (1949); from human pregnancy urine: Lieberman *et al., J. Biol. Chem.* 172, 263 (1948); from human placenta: Pearlman, Cerceo, *ibid.* 194, 807 (1952). Prepn from 20-methyl-Δ^{20}-allopregnen-3β-ol: Koechlin, Reichstein, *Helv. Chim. Acta* 27, 549 (1944); from pregnenolone: Mancera *et al., J. Org. Chem.* 16, 192 (1951); Pappas, Nace, *J. Am. Chem. Soc.* 81, 4556 (1959); by redn of allopregnane-3,20-dione with sodium borohydride: Mancera *et al., ibid.* 75, 1286 (1953); from progesterone 20-cycloethylene ketal: Sondheimer, Klibansky, *Tetrahedron* 5, 15 (1959).
Plates from dil methanol, mp 194-195°. $[\alpha]_D^{17}$ +91.2° (c = 0.4 in ethanol).
Acetate, $C_{23}H_{36}O_3$, plates from methanol, mp 144-146°. $[\alpha]_D^{18}$ +69° (chloroform).

285. Allopregnan-20α-ol-3-one. *20α-Hydroxy-5α-pregnan-3-one;* 20α-hydroxy-3-oxo-5α-pregnane. $C_{21}H_{34}O_2$; mol wt 318.50. C 79.19%, H 10.76%, O 10.05%. Prepn from funtumidine: Janot *et al., Bull. Soc. Chim. France* 1960, 1669.
Crystals, mp 179°. $[\alpha]_D$ +36.6° (c = 0.8 in chloroform).
Acetate, $C_{23}H_{36}O_3$, crystals from ethanol, mp 155°. $[\alpha]_D$ +24° (c = 1.5 in chloroform).

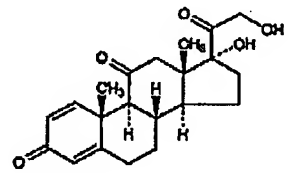
286. Allopregnan-20β-ol-3-one. *20β-Hydroxy-5α-pregnan-3-one;* 20β-hydroxy-3-oxo-5α-pregnane. $C_{21}H_{34}O_2$; mol wt 318.50. C 79.19%, H 10.76%, O 10.05%. Prepn from allopregnane-3β,20β-diol-3-acetate: Rubin *et al. J. Am. Chem. Soc.* 73, 2338 (1951); from isofuntumidine: Janot *et al., Bull. Soc. Chim. France* 1960, 1669.
Crystals from heptane, mp 185°. $[\alpha]_D$ +20° (c = 1.2 in chloroform).
Acetate, $C_{23}H_{36}O_3$, crystals from ethanol, mp 148°. $[\alpha]_D$ +57° (c = 1.9 in chloroform).

1958, 1260; Elks, Phillips, U.S. pat. 2,936,313 (1960 to Glaxo).

White powder. Slightly hygroscopic. Stable at room temp. $[\alpha]_D^{25}$ +102.5°. uv max (methanol): 243 nm ($A_{1cm}^{1\%}$ 308). Sol in water, methanol, ethanol. pH of 1% aq soln 7.5 to 8.5.

THERAP CAT: Glucocorticoid.
THERAP CAT (VET): Glucocorticoid.

7904. Prednisone. *17,21-Dihydroxypregna-1,4-diene-3,11,20-trione;* 1,4-pregnadiene-17α,21-diol-3,11,20-trione; Δ¹-dehydrocortisone; Δ¹-cortisone; deltacortisone; delta E; metacortandracin; retrocortine; NSC-10023; Ancortone; Colisone; Cortancyl; Dacortin; Decortancyl; Decortin; Delcortin; Deltacortone; Deltasone; Deltison; Di-Adreson; Easorton; Meticorten; Nurison; Orasone; Paracort; Prednilonga; Pronison; Rectodelt; Sone; Ultracorten. $C_{21}H_{26}O_5$; mol wt 358.43. C 70.37%, H 7.31%, O 22.32%. Prepn: Oliveto, Gould, U.S. pat. 2,897,216 (1959 to Schering). Microbiological prepn: Nobile *et al, J. Am. Chem. Soc.* 77, 4184 (1955); Nobile, U.S. pat. 2,837,464 and 3,134,718 (1958, 1964 both to Schering); Herzog *et al., Tetrahedron* 18, 581 (1962). Structure: Herzog *et al., Science* 121, 176 (1955); *cf.* Djerassi *et al.*, U.S. pat. 2,579,479 (1951 to Syntex).

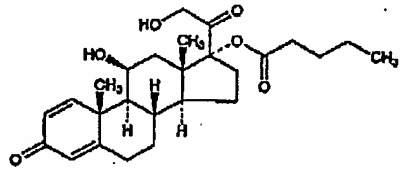


Crystals, dec 233-235°. $[\alpha]_D^{25}$ +172° (dioxane). uv max (methanol): 238 nm (ε 15500). Very slightly sol in water. One gram dissolves in about 150 ml alcohol, in about 200 ml chloroform. Slightly sol in methanol, dioxane.

21-Acetate, $C_{23}H_{28}O_6$, *Delta-Cortelan, Hostacortin.* Crystals, dec 226-232°. $[\alpha]_D^{25}$ +186° (dioxane). uv max (ethanol): 238 nm (ε 16100).

THERAP CAT: Glucocorticoid.
THERAP CAT (VET): Adrenocortical steroid. Glucocorticoid, anti-inflammatory.

7905. Prednival. *(11β)-11,21-Dihydroxy-17-[(1-oxopentyl)oxy]pregna-1,4-diene-3,20-dione; 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 17-valerate;* prednisolone 17-valerate; W-4869. $C_{26}H_{36}O_6$; mol wt 444.57. C 70.24%, H 8.16%, O 21.59%. Prepn: Vitali, Ercoli, *Tetrahedron Letters* 1961, 448; Ercoli, Gardi, U.S. pat. 3,152,154 (1964 to Vismara).

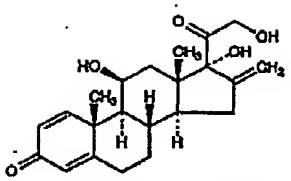


Crystals from aq methanol, mp 210-213°. $[\alpha]_D$ +3.5° (dioxane).

21-Acetate, $C_{28}H_{38}O_7$, *Accprenal.*

THERAP CAT: Glucocorticoid.

7906. Prednylidene. *(11β)-11,17,21-Trihydroxy-16-methylenepregna-1,4-diene-3,20-dione;* $\Delta^{1,4}$-pregnadiene-16-methylene-11β,17α,21-triol-3,20-dione; 16-methylene-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione; 16-methylenprednisolone; Dacortilen; Decortilen; Sterocort. $C_{22}H_{28}O_5$; mol wt 372.46. C 70.94%, H 7.58%, O 21.48%. Prepn: Mannhardt *et al., Tetrahedron Letters* no. 16, 21 (1960). Prepn of the 21-diethylaminoacetate: *idem et al.*, Ger. pat. 1,134,074 (1962 to E. Merck), *C.A.* 58, 568a (1963).

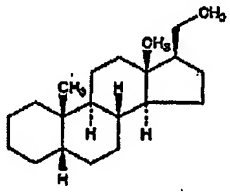


Solid, mp 233-235°. $[\alpha]_D^{25}$ +31° (dioxane). uv max: 240 nm (ε 15900).

21-Diethylaminoacetate hydrochloride, $C_{28}H_{39}NO_6 \cdot HCl$, *Decortilen soluble.* Solid, mp 245-246°. $[\alpha]_D$ +45° (water). uv max (water): 246-247 nm ($E_{1cm}^{1\%}$ 300).

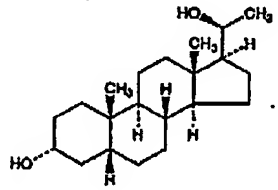
THERAP CAT: Glucocorticoid.

7907. Pregnane. *5β-Pregnane;* 17β-ethyletiocholane. $C_{21}H_{36}$; mol wt 288.52. C 87.42%, H 12.58%. Prepd by reduction of etiocholyl methyl ketone or of pregnanedione. Butenandt, *Ber.* 64, 2529 (1931); Marker *et al., J. Am. Chem. Soc.* 60, 1067 (1938); Steiger, Reichstein, *Helv. Chim. Acta* 21, 161 (1938).



Monoclinic scales, plates from methanol; mp 83.5°. d_4^{25} 1.032. $[\alpha]_D^{25}$ +20° (c = 2 in chloroform).

7908. Pregnanediol. *(3α,5β,20S)-Pregnane-3,20-diol.* $C_{21}H_{36}O_2$; mol wt 320.52. C 78.70%, H 11.32%, O 9.98%. A metabolite of progesterone, present in large amounts in pregnancy urine. Isoln from pregnancy urine of women: Marrian, *Biochem. J.* 23, 1090 (1929), Butenandt, *Ber.* 63, 659 (1930); of cows, mares, and chimpanzees: Fish *et al. J. Biol. Chem.* 143, 716 (1942). Prepn by reduction of pregn-16-ene-3,20-dione: Marker *et al.*, U.S. pat. 2,352,852 (1944 to Parke, Davis). Conversion to progesterone: Butenandt, Schmidt, *Ber.* 67, 1893, 1901 (1934). Conversion to 3α-hydroxypregnan-20-one: Marker, U.S. pat. 2,223,377 (1940 to Parke, Davis). Prepn of the 3-acetate: Hirschmann, *J. Biol. Chem.* 140, 797 (1941); Ralls *et al., ibid.* 210, 709 (1954). Prepn of the 20-acetate: Hirschmann, *loc. cit.* Prepn of the diacetate: Johnson *et al., J. Chem. Soc.* 1954, 1302. Crystal structure: Haner, Norton, *Acta Cryst.* 16, 707 (1963). Review of metabolism, bioactivity and assay during pregnancy: P. J. Keller, *Contrib Gynecol. Obstet.* 2, 75-91 (1976).



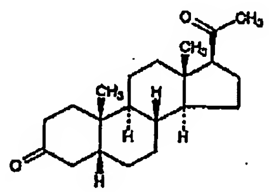
Crystals from acetone or ethanol, mp 238°. $[\alpha]_D^{25}$ +27.4° (c = 0.7 in alc). Sparingly sol in organic solvents. Not precipitated by digitonin.

3-Acetate, $C_{23}H_{38}O_3$, *3α-acetoxypregnan-20α-ol.* Crystals, mp 132°. $[\alpha]_D^{25}$ +45° ($CHCl_3$).

20-Acetate, $C_{23}H_{38}O_3$, *20α-acetoxypregnan-3α-ol.* Crystals, mp 174°.

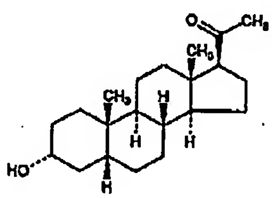
Diacetate, $C_{25}H_{40}O_4$, *3α,20α-diacetoxypregnane.* Crystals from light petroleum, mp 180°, also reported as mp 182-183°. $[\alpha]_D^{15}$ +35° (c = 1.1 in $CHCl_3$).
USE: In manuf of progesterone.

7909. **3,20-Pregnanedione.** *(5β)-Pregnane-3,20-dione.* $C_{21}H_{32}O_2$; mol wt 316.48. C 79.70%, H 10.19%, O 10.11%. From pregnancy urine of mares. Prepn from other steroids: Butenandt, *Ber.* 63, 659 (1930); Butenandt, Fleischer, *Ber.* 68, 2094 (1935); Marker *et al., J. Am. Chem. Soc.* 59, 1595 (1937); Shoppee, Reichstein, *Helv. Chim. Acta* 24, 356 (1941); U.S. pats. 2,160,719; 2,352,852; 2,323,276; 2,229,-818.



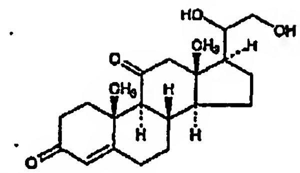
Needles from dil alc, mp 123°. Insol in water. Freely sol in the usual organic solvents.
Dioxime, $C_{21}H_{34}N_2O_2$, dec above 250°.

7910. **Pregnan-3α-ol-20-one.** *(3α,5β)-3-Hydroxypregnan-20-one;* 3α-hydroxy-5β-pregnan-20-one; pregnanolone; eltanolone; KABI 2213. $C_{21}H_{34}O_2$; mol wt 318.50. C 79.19%, H 10.76%, O 10.05%. Naturally occurring metabolite of progesterone, *q.v.* Isoln from urine of pregnant women: R. E. Marker, O. Kamm, *J. Am. Chem. Soc.* 59, 1373 (1937); from bile of pregnant cows: W. H. Pearlman, E. Cerceo, *J. Biol. Chem.* 176, 847 (1948). Prepn: R. E. Marker *et al., J. Am. Chem. Soc.* 59, 1841 (1937); L. Gyermek *et al., J. Med. Chem.* 11, 117 (1968); T. L. G. Lemos, J. D. McChesney, *J. Nat. Prod.* 53, 152 (1990). Pharmacokinetics and pharmacodynamics: P. Carl *et al., Acta Anaesthesiol. Scand.* 38, 734 (1994). Comparative clinical evaluation: J. Van Hemelrijck *et al., Anesthesiology* 80, 36 (1994); H. Eriksson *et al., Acta Anaesthesiol. Scand.* 39, 479 (1995). Hemodynamic effects in humans: J. W. Sear *et al., J. Clin. Anesthesia* 7, 126 (1995).



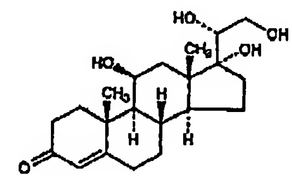
Needles from aq methanol, mp 148-148.5° (Pearlman, Cerceo); also reported as cryst from hexane, mp 131-132° (Lemos, McChesney). $[\alpha]_D^{23}$ +59.6° (c = 0.3 in chloroform). $[\alpha]_D^{24}$ +108.5 ±1° (c = 9.23 mg/1.23 ml abs ethanol). LD_{50} in mice, rats (mg/kg): 66 ± 10, 27.5 ± 2.4 i.v. (Gyermek).
THERAP CAT: Anesthetic (local).

7911. **4-Pregnene-20,21-diol-3,11-dione.** *20,21-Dihydroxypregn-4-ene-3,11-dione;* Reichstein's substance T. $C_{21}H_{30}O_4$; mol wt 346.47. C 72.80%, H 8.73%, O 18.47%. Isoln from adrenal glands: Reichstein, von Euw, *Helv. Chim. Acta* 22, 1222 (1939).



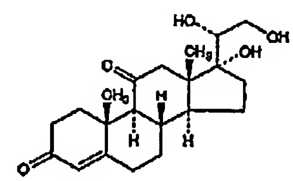
Crystals, mp ~210°. $[\alpha]_D^{10}$ +176° (acetone).
Diacetate, $C_{25}H_{34}O_6$, crystals, mp 212-213°.

7912. **4-Pregnene-11β,17α,20β,21-tetrol-3-one.** *11β,-17,20β,21-Tetrahydroxypregn-4-en-3-one;* 17-(1,2-dihydroxyethyl)androsten-3-one-11,17-diol; Reichstein's substance E. $C_{21}H_{32}O_5$; mol wt 364.48. C 69.20%, H 8.85%, O 21.95%. Occurs in adrenal cortex. Isoln: Reichstein, *Helv. Chim. Acta* 19, 29 (1936); 20, 953 (1937); Reichstein, von Euw, *ibid.* 24, 247E (1941).



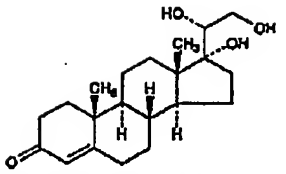
Hydrated crystals from dil acetone, dec 125°. $[\alpha]_D^{20}$ +87° (alc). $[M]_D$ +317°. uv max: 240 nm.
20,21-Diacetate, crystals, dec 229-230°. $[\alpha]_D^{20}$ +162.7°. $[M]_D$ +730° (acetone).

7913. **4-Pregnene-17α,20β,21-triol-3,11-dione.** *(20R)-17,20,21-Trihydroxypregn-4-ene-3,11-dione;* Reichstein's substance U. $C_{21}H_{30}O_5$; mol wt 362.47. C 69.59%, H 8.34%, O 22.07%. Isoln from adrenal glands: Reichstein, von Euw, *Helv. Chim. Acta* 24, 247E (1941).



Clusters of needles from acetone + ether, mp 208-209°.
20,21-Diacetate, $C_{25}H_{34}O_7$, pointed needles from acetone + ether or chloroform + ether, mp 253°. $[\alpha]_D^{21}$ +178.5° (c = 0.924 in acetone). uv max (alc): 239 nm (log ε 4.1). Less sol than the 20,21-diacetate of 4-pregnene-11β,17α,20,21-tetrol-3-one.

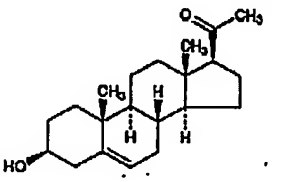
7914. **4-Pregnene-17α,20β,21-triol-3-one.** *(20R)-17,-20,21-Trihydroxypregn-4-en-3-one;* 17-(1,2-dihydroxyethyl)-Δ^4-androsten-3-on-17α-ol; 17α-pregnenetriolone. $C_{21}H_{32}O_4$; mol wt 348.48. C 72.38%, H 9.26%, O 18.36%. Prepd from 17-ethynyltestosterone by hydrogenation with palladium in pyridine, allylic rearrangement, and hydroxylation with osmium tetroxide: Ruzicka, Müller, *Helv. Chim. Acta* 22, 755 (1939); Logemann, *Naturwiss.* 27, 196 (1939); from a 3-enol ester of a 17,21-diacyloxyprogesterone by reduction followed by saponification: Swiss pat. 207,496 (1940), *C.A.* 36, 3636 (1942).



Crystals from methanol, mp 190°. Sol in dioxane, chloroform, methanol. $[\alpha]_D$ +63° (c = 1 in dioxane). uv max: 240 nm (log ε 4.1).

20,21-Diacetate, $C_{25}H_{36}O_6$, crystals from acetone + ether. Polymorphic; mp 170° and 194°; $[\alpha]_D^{20}$ +125° (dioxane). Reaction with zinc in toluene yields 17-isodesoxycorticosterone acetate.

7915. Pregnenolone. *(3β)-3-Hydroxypregn-5-en-20-one;* Δ^5-pregnen-3β-ol-20-one; 17β-(1-ketoethyl)-Δ^5-androsten-3β-ol. $C_{21}H_{32}O_2$; mol wt 316.48. C 79.70%, H 10.19%, O 10.11%. Prepn from stigmasterol: Butenandt *et al., Ber.* 67, 1611 (1934); Butenandt, Fleischer, *Ber.* 70, 96 (1937); from androstenolone: H. Butenandt, J. Schmidt-thome, *Ber.* 72, 182 (1939); S. Danishefsky *et al., J. Org. Chem.* 40, 1989 (1975); from Δ^5-3-acetoxyetiocholenic acid chloride: Wettstein, *Helv. Chim. Acta* 23, 1373 (1940); from diosgenin: Marker, Krueger, *J. Am. Chem. Soc.* 62, 3349 (1940); Marker *et al., ibid.* 69, 2173 (1947); from nologenin: *eidem, ibid.* 2395; by treating a 21-halo-Δ^5-pregnen-3-ol-20-one with a reducing agent: Swiss pat. 215,139 (1941), *C.A.* 42, 3144 (1948). Crystal structure: J. Bordner *et al., Cryst. Struct. Commun.* 7, 513 (1978).

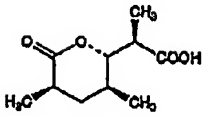


Needles from dil alc, mp 193°. $[\alpha]_D^{20}$ +28° (alc). Very sparingly sol in water. Sol'y (g/100 ml of soln): carbon tetrachloride 0.5; petr ether 0.1; ethyl acetate 1.1; acetone 0.6; chloroform 17.0; ethanol 1.9; benzene 0.9; isopropanol 1.5. Sol'y (g/100 ml of solvent): propylene glycol 0.1; dioxane 3.1; benzyl alcohol 8.1. On refluxing with methyl alcohol yields the 17-isopregnenolone, mp 172-173°, $[\alpha]_D^{25}$ −140.5° (alcohol).

Acetate, $C_{23}H_{34}O_3$, needles from alcohol, mp 149-151°. $[\alpha]_D^{20}$ +22° (alcohol). Sol'y (g/100 ml of soln): carbon tetrachloride 5.0; petr ether 1.0; ethyl acetate 7.9; acetone 2.7; chloroform 55.0; ethanol 2.5; benzene 26.0; isopropanol 2.0. Sol'y (g/100 ml of solvent): propylene glycol 0.1; dioxane 20.2; benzyl alcohol 11.1; benzyl benzoate 9.1.

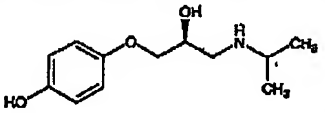
Methyl ether, $C_{22}H_{34}O_2$, crystals from abs or dil methanol, mp 123.5°. $[\alpha]_D^{25}$ +18° (c = 1.085 in chloroform).

7916. Prelog-Djerassi Lactone. *[2S-[2α(S*),3β,5β]]-Tetrahydro-α,5,5-trimethyl-6-oxo-2H-pyran-2-acetic acid;* (+)-Prelog-Djerassi lactonic acid; 6-(1-carboxyethyl)-3,4,5,6-tetrahydro-3,5-dimethyl-2-pyranone. $C_{10}H_{16}O_4$; mol wt 200.23. C 59.98%, H 8.05%, O 31.96%. Intermediate in the synthesis of macrolide antibiotics. Isoln as degradation product of narbomycin, *q.v.*: R. Anliker *et al., Helv. Chim. Acta* 39, 1785 (1956); of methymycin, *q.v.*: C. Djerassi, J. A. Zderic, *J. Am. Chem. Soc.* 78, 6390 (1956). Abs config: R. W. Rickards, R. M. Smith, *Tetrahedron Letters* 1970, 1025. Synthesis: P. A. Grieco *et al., J. Am. Chem. Soc.* 101, 4749 (1979); D. A. Evans, J. Bartroli, *Tetrahedron Letters* 23, 807 (1982). Synthesis of (±)-form: S. Masamune *et al., J. Am. Chem. Soc.* 97, 3512 (1975); C. Santelli-Rouvier *et al., Tetrahedron Letters* 35, 6101 (1994). Review of stereoselective syntheses: S. F. Martin, D. E. Guinn, *Synthesis* 1991, 245.



Crystals, mp 124-125°. $[\alpha]_D$ +33° (c = 0.797 in $CHCl_3$).

7917. Prenalterol. *(S)-4-[2-Hydroxy-3-[(1-methylethyl)-amino]propoxy]phenol;* (−)-(S)-1-(p-hydroxyphenoxy)-3-(isopropylamino)-2-propanol. $C_{12}H_{19}NO_3$; mol wt 225.29. C 63.98%, H 8.50%, N 6.22%, O 21.31%. A β_2-adrenergic agonist. Prepn: K. A. Jaeggi *et al.*, Ger. pat. 2,503,968 corresp to U.S. pats. 3,978,041 and 4,049,797 (1974, 1976, 1977, all to Ciba-Geigy). Pharmacologic study: E. Carlsson *et al., Arch. Pharmacol.* 300, 101 (1977). Metabolism, hemodynamic effects, pharmacokinetics in man: O. Rönn *et al., Eur. J. Clin. Pharmacol.* 17, 81 (1980). Cardiovascular effects: D. H. Scott *et al., Brit. J. Clin. Pharmacol.* 7, 365 (1979). Clinical study in coronary heart disease: I. Hutton *et al., Brit. Heart J.* 43, 134 (1980). *See also* T. P. Kenakin, D. Beek, *J. Pharmacol. Exp. Ther.* 213, 406 (1980) for a discussion of the selectivity of action. Prepns of the racemic mixture: Neth. pat. Appl. 6,409,883 corresp to H. Köppe *et al.*, U.S. pat. 3,637,852 (1965, 1972 both to Boehringer, Ing.); Neth. pat. Appl. 301,580 corresp to A. F. Crowther, L. H. Smith, U.S. pat. 3,501,769 (1965, 1970 both to ICI); A. F. Crowther *et al., J. Med. Chem.* 12, 638 (1969). Symposium: *Acta. Med. Scand.*, suppl. 659, 1-325 (1982).

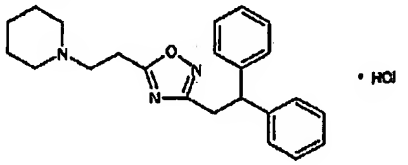


Crystals from ethyl acetate, mp 127-128°. $[\alpha]_D^{25}$ −1° ±1°; $[\alpha]_{546}^{25}$ +2° ±1° (c = 0.940 in methanol).

Hydrochloride, $C_{12}H_{19}NO_3.HCl$, *H-133/22, CGP-7760B, (−)-H-80/62, Hyperen, Varbtan.*

THERAP CAT: Cardiotonic.

7918. Prenoxdiazine Hydrochloride. *1-[2-[3-(2,2-Diphenylethyl)-1,2,4-oxadiazol-5-yl]ethyl]piperidine monohydrochloride;* 3-(β,β-diphenylethyl)-5-(β-piperidinoethyl)-1,2,4-oxadiazole hydrochloride; HK-256; Libexin; Lomapect; Tibexin. $C_{25}H_{29}ClN_3O$; mol wt 397.95. C 69.42%, H 7.09%, Cl 8.91%, N 10.56%, O 4.02%. Prepn: K. Harsanyi *et al.*, Hung. pat. 151,748 (1964 to Chinoin), *C.A.* 62, 11821f (1965). Pharmacology: L. Tardos, I. Erdély, *Arzneimittel-Forsch.* 16, 617 (1966). Stability study: E. Pandula *et al., Acta Pharm. Hung.* 38, 68 (1968). Review of pharmacology and clinical studies: K. Harsanyi *et al., Boll. Chim. Farm.* 112, 691 (1973).



Crystals from ethanol, mp 192-193°. LD_{50} in mice, rats (mg/kg): 920, >2000 orally; 34, 32 i.v. (Tardos, Erdély).

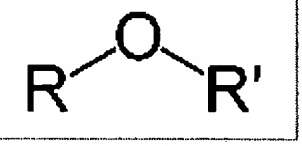
THERAP CAT: Antitussive.

7919. Prenylamine. *N-(1-Methyl-2-phenylethyl)-γ-phenylbenzenepropanamine; N-(3,3-diphenylpropyl)-α-methylphenethylamine; N-*(3'-phenyl-2'-propyl)-1,1-diphenyl-3-propylamine; 1-phenyl-2-[1',1'-diphenylpropyl-3'-amino]-propane; B-436; Elecor. $C_{24}H_{27}N$; mol wt 329.49. C 87.49%, H 8.26%, N 4.25%. Prepn: G. Ehrhart *et al.*, Ger. pat. 1,100,031, *C.A.* 56, 3413h (1962) and Ger. pat. 7,111,

Ether

From Wikipedia, the free encyclopedia

Ether is a class of chemical compounds which contain an ether group — an oxygen atom connected to two (substituted) alkyl or aryl groups — of general formula **R–O–R'**.[1] A typical example is the solvent and anesthetic diethyl ether, commonly referred to simply as "ether" (ethoxyethane, CH_3-CH_2-O-CH_2-CH_3).



The general structure for an ether

Contents

Physical properties

Ether molecules cannot form hydrogen bonds among each other, resulting in a relatively low boiling point comparable to that of the analogous alcohols. However, the differences in the boiling points of the ethers and their isometric alcohols become smaller as the carbon chains become longer, as the hydrophobic nature of the carbon chain becomes more predominant over the presence of hydrogen bonding.

Ethers are slightly polar as the R - C - O - C - Z bond angle in the functional group is about 110 degrees, and the C - O dipole does cancel out. Ethers are more polar than alkenes but not as polar as alcohols, esters or amides of comparable structure. However, the presence of two lone pairs of electrons on the oxygen atoms makes hydrogen bonding with water molecules possible, causing the solubility of alcohols (for instance, butan-1-ol) and ethers (ethoxyethane) to be quite dissimilar.

Cyclic ethers such as tetrahydrofuran and 1,4-dioxane are totally miscible in water because of the more exposed oxygen atom for hydrogen bonding as compared to aliphatic ethers.

Ethers can act as Lewis bases. For instance, diethyl ether forms a complex with boron compounds, such as boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$). Ethers also coordinate to magnesium in Grignard reagents (RMgBr).

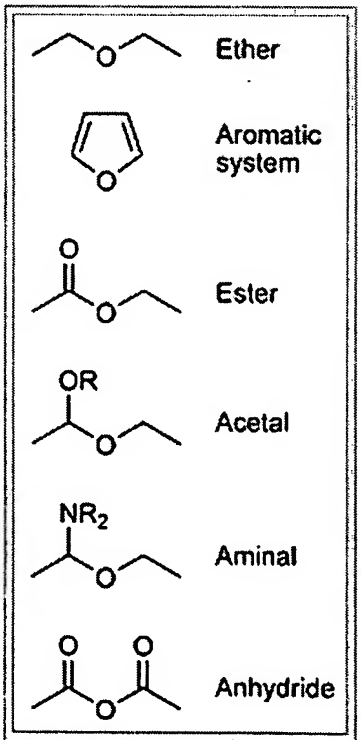
Nomenclature

In the IUPAC nomenclature system, ethers are named using the general formula *"alkoxyalkane"*, for example CH_3-CH_2-O-CH_3 is methoxyethane. If the ether is part of a more complex molecule, it is described as an alkoxy substituent, so -OCH_3 would be considered a *"methoxy-"* group. The simpler alkyl radical is written in front, so CH_3-O-CH_2CH_3 would be given as *methoxy*(CH_3)*ethane*(CH_2CH_3). The nomenclature of describing the two alkyl groups and appending *"ether"*, e.g. *"ethyl methyl ether"* in the example above, is a trivial usage.

Similar structures

Ethers are not to be confused with the following classes of compounds with the same general structure R-O-R.

- Aromatic compounds like furan where the oxygen is part of the aromatic system.
- Compounds where one of the carbon atoms next to the oxygen is connected to oxygen, nitrogen, or sulfur:
  - Esters R-C(=O)-O-R
  - Acetals R-CH(-O-R)-O-R
  - Aminals R-CH(-NH-R)-O-R
  - Anhydrides R-C(=O)-O-C(=O)-R

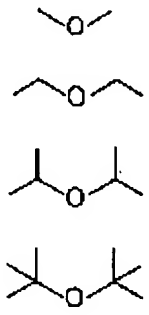


Not all compounds of the formula R-O-R are ethers.

Primary, secondary, and tertiary ethers

The terms *"primary ether"*, *"secondary*

ether", and *"tertiary ether"* are occasionally used and refer to the carbon atom next to the ether oxygen. In a *primary ether* this carbon is connected to only one other carbon as in diethyl ether CH_3-CH_2-O-CH_2-CH_3. An example of a *secondary ether* is diisopropyl ether $(CH_3)_2CH$-O-$CH(CH_3)_2$ and that of a *tertiary ether* is di-tert-butyl ether $(CH_3)_3C$-O-$C(CH_3)_3$.



Dimethyl ether, a *primary*, a *secondary*, and a *tertiary ether*.

Polyethers

Polyethers are compounds with more than one ether group. While the term generally refers to polymers like polyethylene glycol and polypropylene glycol, low molecular compounds such as the crown ethers may sometimes be included.

Organic reactions

Synthesis

Ethers can be prepared in the laboratory in several different ways.

- Intermolecular Dehydration of alcohols:

  $R\text{-}OH + R\text{-}OH \rightarrow R\text{-}O\text{-}R + H_2O$
  This direct reaction requires drastic conditions (heating to 140 degrees Celsius and an acid catalyst, usually concentrated sulfuric acid). Effective for making symmetrical ethers, but not as useful for synthesising asymmetrical ethers because the reaction will yield a mixture of ethers, making it usually not applicable:

  $3R\text{-}OH + 3R'\text{-}OH \rightarrow R\text{-}O\text{-}R + R'\text{-}O\text{-}R + R'\text{-}O\text{-}R' + 3H_2O$

  Conditions must also be controlled to avoid overheating to 170 degrees which will cause intramolecular dehydration,a reaction that

yields alkenes. In addition, the alcohol must be in excess.

$R\text{-}CH_2\text{-}CH_2(OH) \rightarrow R\text{-}CH{=}CH_2 + H_2O$

Such conditions can destroy the delicate structures of some functional groups. There exist several milder methods to produce ethers.

- Nucleophilic displacement of alkyl halides by alkoxides

$R\text{-}O^- + R\text{-}X \rightarrow R\text{-}O\text{-}R + X^-$
This reaction is called the Williamson ether synthesis. It involves treatment of a parent alcohol with a strong base to form the alkoxide anion followed by addition of an appropriate aliphatic compound bearing a suitable leaving group (R-X). Suitable leaving groups (X) include iodide, bromide, or sulfonates. This method does not work if R is aromatic like in bromobenzene ($Br\text{-}C_6H_5$), however, if the leaving group is separated by at least one carbon from the benzene, the reaction should proceed (as in $Br\text{-}CH_2\text{-}C_6H_5$). Likewise, this method only gives the best yields for primary carbons, as secondary and tertiary carbons will undergo E2 elimination on exposure to the basic alkoxide anion used in the reaction due to steric hindrance from the large alkyl groups. Aryl ethers can be prepared in the Ullmann condensation.

- Nucleophilic Displacement of Alkyl halides by phenoxides

The R-X cannot be used to react with the alcohol. However, phenols can be used to replace the alcohol, while maintaining the alkyl halide. Since phenols are acidic, they readily react with a strong base like sodium hydroxide to form phenoxide ions. The phenoxide ion will then substitute the -X group in the alkyl halide, forming an ether with an aryl group attached to it in a reaction with an SN2 mechanism.

$HO\text{-}C_6H_5 + OH^- \rightarrow O^-\text{-}C_6H_5$

$O^-\text{-}C_6H_5 + R\text{-}X \rightarrow R\text{-}O\text{-}C_6H_5$

- Electrophilic addition of alcohols to alkenes.

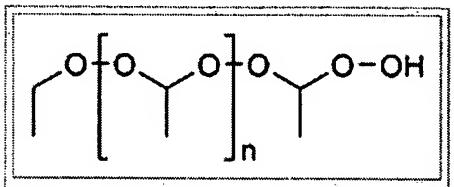
$R_2C{=}CR_2 + R\text{-}OH \rightarrow R_2CH\text{-}C(\text{-}O\text{-}R)\text{-}R_2$
Acid catalysis is required for this reaction. Often, Mercury trifluoroacetate ($Hg(OCOCF_3)_2$ is used as a catalyst for the reaction, creating an ether with Markovnikov regiochemistry. Tetrahydropyranyl ethers are used as protective groups for alcohols.

Cyclic ethers which are also known as epoxides can be prepared:

- By the oxidation of alkenes with a peroxyacid such as m-CPBA.
- By the base intramolecular nuclephilic substitution of a halohydrin.

Reactions

Ethers in general are of very low chemical reactivity. Organic reactions are:



Structure of the polymeric diethyl ether peroxide

- Hydrolysis.

  Ethers are hydrolyzed only under drastic conditions like heating with boron tribromide or boiling in hydrobromic acid. Lower mineral acids containing a halogen, such as hydrochloric acid will cleave ethers, but very slowly. Hydrobromic acid and hydroiodic acid are the only two that do so at an appreciable rate. Certain aryl ethers can be cleaved by aluminium chloride.

- Nucleophilic displacement.

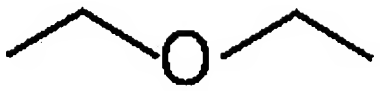
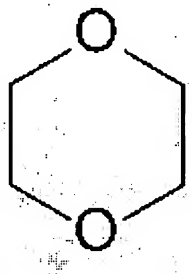
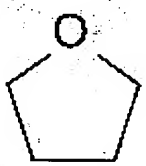
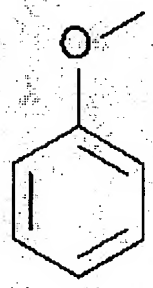
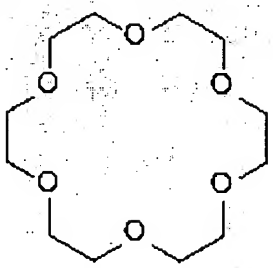
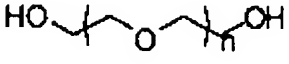
  Epoxides, or cyclic ethers in three-membered rings, are highly susceptible to nucleophilic attack and are reactive in this fashion.

- Peroxide formation.

  Primary and secondary ethers with a CH group next to the ether oxygen easily form highly explosive organic peroxides (e.g. diethyl ether peroxide) in the presence of oxygen, light, and metal and aldehyde impurities. For this reason ethers like diethyl ether and THF are usually avoided as solvents in industrial processes

Important ethers

	Ethylene oxide	The smallest cyclic ether.
	Dimethyl ether	An aerosol spray propellant.
	Diethyl ether	A common low boiling solvent

		(b.p. 34.6°C).
	Dimethoxyethane (DME)	A high boiling solvent (b.p. 85° C):
	Dioxane	A cyclic ether and high boiling solvent (b.p. 101.1°C).
	Tetrahydrofuran (THF)	A cyclic ether, one of the most polar simple ethers that is used as a solvent.
	Anisole (methoxybenzene)	An **aryl ether** and a major constituent of the essential oil of anise seed.
	Crown ethers	Cyclic polyethers that are used as phase transfer catalysts.
	Polyethylene glycol (PEG)	A linear polyether, e.g. used in cosmetics:

See also

- Functional group
- Methoxy
- Petroleum ether, not an ether but a low boiling alkane mixture.
- Thioether, analogs of ethers with the oxygen replaced by sulfur.
- Luminiferous ether

References

1. ^ International Union of Pure and Applied Chemistry. "ethers". *Compendium of Chemical Terminology* Internet edition.

External links

- ILPI page about ethers.
- An Account of the Extraordinary Medicinal Fluid, called Aether, by M. Turner, circa 1788, from Project Gutenberg

Activity of 3-methoxy-pregnenolone on progesterone receptor

The capacity of 3-methoxy-pregnenolone to display progesterone activity, and thus to be considered as a progestin, was tested by assaying the activity of 3-methoxy-pregnenolone on progesterone receptor.

Indeed, progesterone is an agonist of progesterone receptor, as are all progestins. In contrast, compounds able to inhibit progesterone activity on its receptor are called progesterone receptor antagonists.

Methods

The main experimental setting used is the following: HEK293T cells were transiently transfected, using calcium phosphate precipitation technology, with expression vectors pSG5hPR (which permits expression of human progesterone receptor(PR)), pFC31-luc (contains the luciferase gene under the control of the MMTV promoter, which is in turn activated by binding of a progestin to progesterone receptor) and pcbetagal (which permits expression of betagalactosidase), and cultured during 24 hours with increasing amounts of various compositions:

1. Test of progesterone receptor agonist activity: transfected cells were cultured with increasing amounts of progesterone or 3-methoxy-pregnenolone

   With this setting, a compound with progesterone receptor agonist activity permits a transactivation activity resulting in the expression of luciferase (since the binding of a progestin to PR results in activation of the MMTV promoter, which directs the expression of luciferase).

   In contrast, a compound without progesterone receptor agonist activity does not permit a transactivation activity and luciferase is not expressed (since PR is not activated and thus does not activate the MMTV promoter);

2. Test of progesterone receptor agonist activity: transfected cells were cultured with progesterone (1 nM) and increasing amounts of RU486 (a well-known progesterone receptor antagonist) or 3-methoxy-pregnenolone.

   With this setting, a compound with progesterone receptor antagonist activity competes with progesterone for the occupation of progesterone receptor and results in a progressive loss of transactivation activity when the amount of this compound is increased compared to progesterone.

Results

The results obtained with experimental setting 1 (test of progesterone receptor agonist activity) are displayed in following Figure 1.

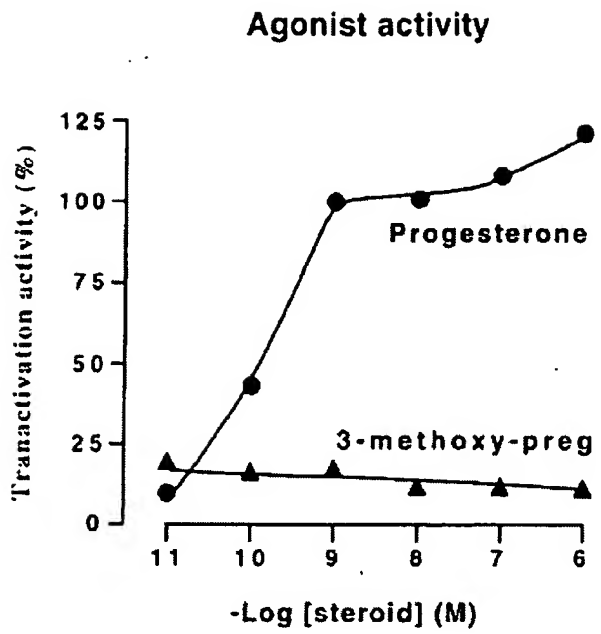


Figure 1. Test of progesterone receptor agonist activity

Figure 1 clearly shows that, contrary to progesterone, which permits a transactivation activity leading to the expression of luciferase, 3-methoxy-pregnenolone does not permit such a transactivation activity, even at the highest tested concentrations, thus demonstrating that 3-methoxy-pregnenolone does not have progesterone receptor agonist activity, and cannot thus be considered as a progestin.

The results obtained with experimental setting 2 (test of progesterone receptor antagonist activity) are displayed in following Figure 2.

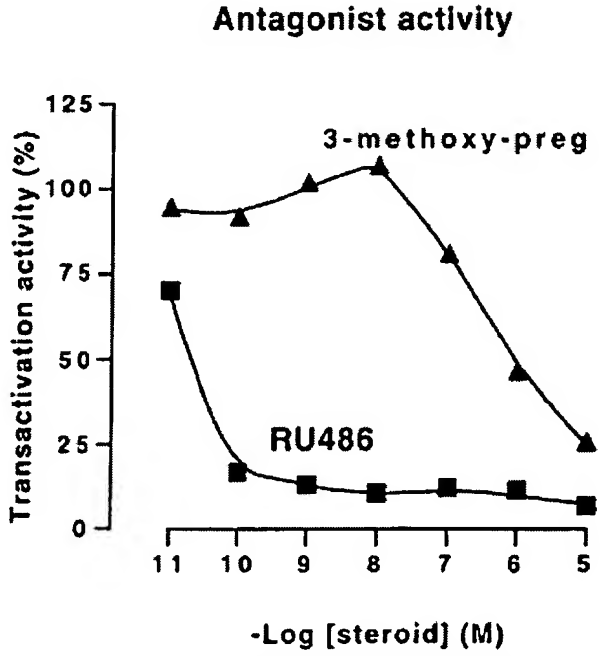


Figure 2. Test of progesterone receptor antagonist activity

These results unambiguously show that even if 3-methoxy-pregnenolone does not have the very high antagonist activity of RU486, it is a weak progesterone receptor antagonist.

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Review

Application of (quantitative) structure–activity relationships to progestagens: from serendipity to structure-based design

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Abstract – Progestagens are drugs, which are widely used in hormonal contraception and in hormone-replacement therapy. Since the natural hormone, progesterone, lacks oral activity, much effort has been devoted to finding analogues with improved oral activity and, preferably, higher potency and selectivity. A crystal structure of the hormone binding domain (HBD) region of the progesterone receptor (PR) could only be obtained recently. For more than forty years the process of designing new progestagens could therefore only be guided by the knowledge of the structure of the ligand and its corresponding in vitro/in vivo activities. While in early days chemical intuition and simple statistics (structure–activity relationship – SAR) were leading the drug design process, in later days more complex statistics and visualization tools have become routinely part of quantitative structure–activity relationship (QSAR) studies. The present review aims to provide a general overview of the strategies, efforts and achievements of synthetic and computational chemists in more than forty years of development of progestagens.

progestagens / contraception / hormone replacement therapy / quantitative structure–activity relationship / hormone binding domain

1. Historical introduction

Early in the 20th century it was found that the corpus luteum in mammals is required for the nidation of fertilized eggs and for maintenance of pregnancy. The compound responsible for this effect was found to be a steroid hormone for which, in 1935, the now generally accepted name progesterone (1) was proposed. Much interest in progesterone was generated by its ability to inhibit ovulation in rats, rabbits and guinea-pigs. This observation ultimately led to the discovery of the contraceptive pill ('The Pill'), which is generally attributed to the American biologist Pincus (1903–1967). Since progesterone itself has poor drug properties, much research has been devoted to the discovery of progesterone mimics (progestagens, alternatively called progestins or progestogens) with improved oral bioavailibility and potency. Over the years several highly orally active progestagens have been discovered, leading to widespread use of these hormones in contraception, but also in HRT (hormone replacement therapy), in treatment of certain cancers, in gynaecological disorders, etc.

Because of their limited amount of flexibility, progestagens, as steroids in general, have always represented an optimal target for structural activity relationship studies. It is therefore not surprising that the rational design of these compounds has evolved from sheer trial and error to various levels of sophistication. In this paper the various SAR approaches which have been applied to progestagens are reviewed.

2. From the origin till the end of the eighties

2.1. Laying the foundations

While progesterone originally was a scarce and very expensive compound, it became readily available in the 1940s after the pioneering work by Marker on the production of steroid hormones from sapogenins. A serious drawback of the natural hormone, however, is its

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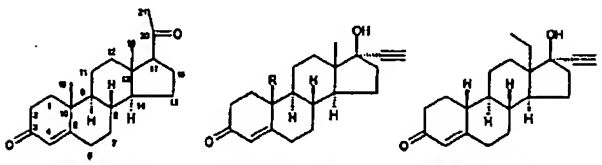
poor bioavailibility on oral administration due to rapid metabolism in the liver: over 99% of the orally administered dose is metabolized in the liver before it reaches the general circulation. The primary goal of the research on new progestagens was therefore to design orally active compounds. Prior to the development of in vitro assays in the 1970s the design of new progestagens was guided by in vivo progestagenic activity. Many different tests have been employed for this purpose, which often makes direct comparison of the potency of compounds tested by different research groups difficult. A reliable and widely accepted test for progestagenic activity is the McPhail test in oestrogen primed immature rabbits. In this test the proliferation of the endometrium is checked upon progestagenic treatment. After a few days of such treatment the differentiation of the endometrium is analysed by autopsy and scored from 0–4, depending on the strength of the effect (progestagenic potency) observed.

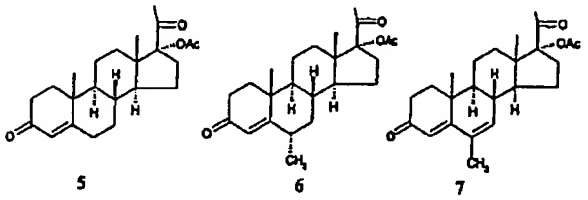
Early research benefited from the application of new synthetic methods in steroid chemistry as well as from insight in the metabolism of progesterone. The first factor is responsible for the serendipitous discovery of ethisterone (2) in 1938 by Inhoffen [1]. This compound unexpectedly turned out to possess oral progestagenic activity, but its practical use was limited due to its androgenic activity. Nevertheless, the finding that the combination of a 17α-ethinyl and a 17β-hydroxyl group appears to mimic the 17β-acetyl group of progesterone and confers a measure of metabolic stability on the steroid has made ethisterone the prototype for a very large family of progestagens. Thus, the 19-nor derivative, norethisterone or norethindrone (3), reported in 1954 by Djerassi [2], turned out to be a much more potent and selective progestagen, which is still in use today. The 19-nor-18-homo derivative of 2 was reported in 1964 by Smith [3] and turned out to be even more potent. The natural enantiomer, known as levonorgestrel (4), is still widely used today.



1 progesterone 2 R = CH_3 ethisterone 3 R = H norethisterone 4 (levo)norgestrel

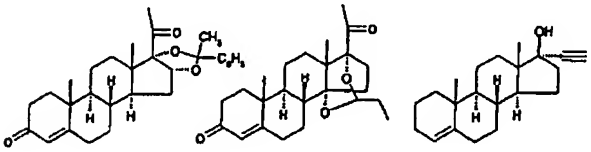
The metabolic degradation of progesterone was shown to involve primarily reduction of the 20-keto group and the 4,5-double bond, followed by reduction of the 3-keto group.

This knowledge allowed the rational design of orally active analogues of progesterone: the 20-keto group could be protected by additional substituents in close proximity, e.g. at C-17 (acyl, alkyl, halogen), C-16 (alkyl, cycloalkyl) and C-21 (OH, alkyl, halogen). Similarly reduction of the A-ring is slowed down by substituents at C-6 (methyl, halogen) and by extending the enone with an additional double bond. Examples are 17α-acetoxyprogesterone (5) [4], medroxyprogesterone acetate (6) [5], megestrol acetate (7) [6], chlormadinone acetate [7], and cyproterone acetate [8].



5 6 7

Oral activity was also improved by inversion of the stereochemistry at C-9 and C-10, resulting in so called retrosteroids such as dydrogesterone [9]. Apart from improved oral bioavailibility, these compounds turned out, in many cases, to have higher intrinsic progestational activity in comparison to progesterone as well. Further orally active progestagens discovered were acetals derived from 16α, 17α-dihydroxyprogesterone (algestone), such as the acetophenide 8 [10], and from 14α, 17α-dihydroxyprogesterone, such as proligestone 9 [11]. Also lynestrenol (10), the 3-desoxoderivative of norethisterone turned out to be an orally active progestagen [12] due to metabolic conversion into 3.



8 9 10

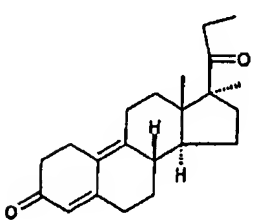
In 1968 over 20 progestagens had found practical use and several hundreds more had been tested. The data have been compiled comprehensively by Neumann [13].

These data provided a sound basis for SAR studies in later decades. Some qualitative conclusions, with regard to SAR that could be drawn were: 1) hydrogen bond accepting substituents at C-3 and C-17 are required; 2) very polar substituents are unfavourable at almost all other positions; 3) small lipophilic substituents are allowed in many positions and often favourable; 4) large substituents are allowed underneath the steroid D-ring,

suggesting the presence of a sizeable pocket in the, at the time putative, progesterone receptor.

It should be noted that up to this point the SAR studies were based on in vivo activities, which were not only dependent on the intrinsic activities of the compounds being studied, but also on metabolic stability and pharmacokinetic properties. Therefore, the SAR relationships found were actually describing a combination of properties rather than a single molecular characteristic. This was changed in the early 1970s when it was discovered that certain tissues contain a protein that binds progesterone with high affinity and was subsequently identified as the progesterone receptor. This discovery made it possible to determine the receptor binding affinity of many steroids via a relatively fast and easy in vitro assay [14–20]. In most cases binding affinities were determined by competition with progesterone, promegestone (R 5020) (11) or Org 2058 (12) and reported as percentages relative to the reference compound.

For many steroids the receptor binding data have been tabulated in graphical [17] or numerical form [16, 21, 22].



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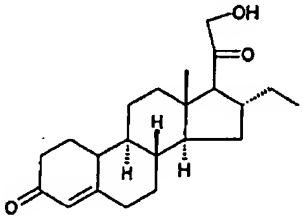

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2.2. SAR methods

The idea of exploring the relationship between molecular structure and physical chemical properties was first introduced in 1935 by Hammett [23] and further developed by Hansch and Fujita [24] in 1964. By introducing the substituent constant π (octanol/water partition coefficient) in Hammett's equation they paved the way for the use of physical-chemical parameters (lipophilicity π, the Taft parameters Es and σ, etc.) for the prediction of biological activities. This type of analysis (parameters π, Es, σ, etc. in combination with a multiple linear regression technique) became rapidly famous as the Hansch analysis and it played a pivotal role in (Q)SAR studies for decades. In the same year, Free and Wilson [25] published a mathematical model based on the additive contribution of the individual fragments present into the molecule to the corresponding activity. This approach, the Free-Wilson approach, was applied with reasonable success to congeneric data sets through the years as well.

At the same time that these SAR techniques were developed, steroids were synthesized in large numbers and tested. Because of their limited flexibility and great chemical diversity, these compounds became an immediate target for SAR studies. A sudden urgency to come to the molecular descriptors or physical-chemical parameters, which would describe their activities, rapidly developed.

As a consequence, a debate soon arose. In 1973, Teutsch and Shapiro [26] published a work on a series of Δ6-6-substituted progestagens where they emphasized the importance of the steric influence of substituents on their activities. One year later, Wolff and Hansch [27] criticized their work by showing that by means of the multiparameter regression technique applied to a set of 13 steroids the hydrophobic and the electron withdrawing descriptors were the best descriptors.

In answer to Hansch, Topliss and Shapiro [28] showed that Hansch analysis was biased by the omission of one outlier and that if the whole original dataset of 14 steroids was considered a two-term equation including hydrophobic and steric effects would best describe the activities. The same year, 1975, Wolff, Hansch, Kollman and Duax [29] repeated the same analysis on another dataset of 9α glucocorticoids and progestagens and showed that their activities were best described by a combination of hydrophobicity and molar refractivity parameters.

One year later, Coburn and Solo [30] criticized again the original work of Wolff and Hansch on Δ6-6-substituted progestagens by repeating the analysis with hydrophobic, electronic and many steric parameters. The conclusion was that steric parameters are important for the description of steroidal activities.

In 1977, Lee et al. [31] performed a step-wise linear regression analysis on the binding affinities to the progesterone receptor of a set of 55 progestagens where they showed how strongly the molecular surface area is correlated with hydrophobicity in this class of compounds.

This debate was not conclusive with respect to the best (combination of) descriptor(s) to be used for steroids in SAR studies, but (a posteriori) it reflects the amount of attention that this new class of compounds was receiving.

Methods other than Hansch and Free-Wilson analyses such as pattern recognition methods were also applied [32]. Moriguchi applied the Adaptive Least-Squares (ALS) and the Linear Discriminant Analysis (LDA) methods to rank with moderate success several datasets of compounds (among which steroids). These methods turned out to be most useful when potencies are ordered

in an ordinal (sequential) scale or when the activity is given by the kind of action.

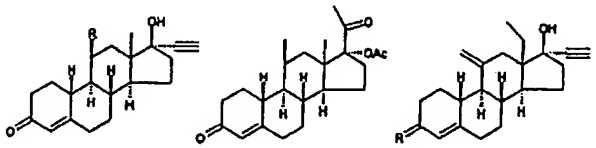
2.3. Crystal structures and steroid binding mechanism models

While the 'Δ6-6-substituted progestagens' debate was progressing, a large number of crystal structures of steroids were determined with the objective of elucidating the working mechanisms of these compounds. The first attempts to rationalize the A, B, C and D rings puckering and strain energies in terms of the substituent or saturation present in the steroidal skeleton were performed with little success. The work of Altona [33, 34] may serve as a typical example. Some time later, Duax, not satisfied with Altona's results, decided to approach the problem statistically by analysing A and D ring puckering as a function of substituents in large data sets of crystal structures.

Duax theory on the working mechanism of steroids started to develop from these studies [35–38]. In his view, subtle conformational changes in the steroidal skeleton were determining the biological activities of these compounds and upon binding all steroids would assume the same 'active' conformation. Further, the A ring (and the substituent on position 3 on it) would determine the binding of the steroid to the receptor, while the D ring would determine its function (agonistic and antagonist activity). This was first concluded from the observation that most chemical and structural variation, on average, is present on the D ring, while only few possibilities for binding are present on the A ring. The D ring would therefore induce the allosteric form of the receptor. Contact of the D ring with a base pair in DNA for activation and transcription factors was also considered.

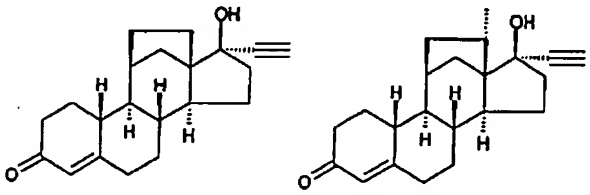
While Duax was persisting in his vision on the working mechanisms of steroids, other ideas contrasting with such vision and supporting the 'induced-fit model' started to develop. The work of Zeelen [39, 40] is one example. From his and other QSAR studies, Zeelen concluded that there is not one specific conformation of the rings in steroids that corresponds to the 'active' conformation. Depending on substituent(s) and/or saturation(s) present on the skeleton the steroid will adopt a conformation, which will be adapted (induced-fit) in the binding cavity of the receptor. In other words, steroids will not adopt upon binding the same 'binding' conformation, but the substituents and/or structural modifications present on the steroidal skeleton will determine their conformations. Such conformations will be accommodated in the binding cavity through a synergistic fit between ligand and receptor. Through the years, many studies (from the work of Bohl and Kaufmann [41, 42] till recently the work of Broess and Groen [43, 44]) strongly supported the induced-fit model.

11-Substituted steroids form a case in point. It was found that 11β-substitution (alkyl, halogen) in many cases leads to greatly enhanced progestational activity. Also short 11-alkylidene substituents, e.g. a methylene group, give a major increase in activity, but not an 11α-substituent [45]. This led to the development of several highly active progestagens, which have found widespread use, i.e. norgestomet (**14**) in veterinary medicine, etonogestrel (**15**) for contraception via non-oral routes and desogestrel (**16**) for oral contraception.



13 **14** **15** R = O; **16** R = H_2

It was found by X-ray crystallography that the steroid skeleton in **13** (R = alkyl, halogen) is curved downward markedly in comparison with the parent compound. This bending of the steroid is obviously due to the repulsion between the 11β substituent and the angular methyl group at C-13. It was speculated that this bending put the 3-keto group in a more favourable position for binding to the progesterone receptor. However, recently norethisterone derivatives **17** and **18** were synthesized, which are bridged analogues of **13**, and they were found to be equally potent progestagens, in spite of the fact that the bridge caused a curvature in the 'wrong' upward direction.



17 **18**

2.4. Molecular mechanics calculations and ^{13}C-chemical shifts

While crystal structures of steroids were determined, Allinger [46] was testing his first versions of the MM force field on them. Structural factors (bond lengths, angles and dihedral angles) as well as reaction rates for

congeneric series were calculated with MM and compared with the corresponding experimental data.

Allinger's attempt to obtain correct in silico structures of steroids could not pass unobserved. Duax [37, 38] performed an extended analysis on conformer populations of steroids from crystal structures and MM calculations. His conclusions were that crystal structures outperform MM calculations because MM yielded correct bond distances and angles, but deviated as much as 50° from the crystal structure in the estimate of the dihedral angles. Relative energies of compounds turned out to be off by at least a factor of 10. Duax concluded that the program of Allinger, MM2p, needed improvement and that the information taken from crystallography could help that process.

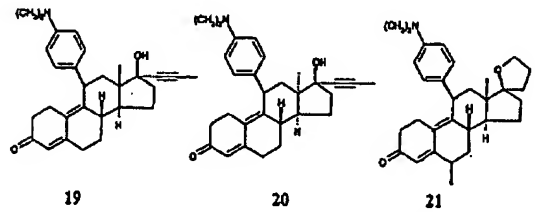
The work of Allinger was a breakthrough. Schneider and Gschwendtner [47–49] performed several MM calculations on steroids in order to come to a better understanding of the substituent effects on the different rings of the steroidal skeleton and more specifically of the polar and steric through-bond transmission change mechanisms. In these investigations they often combined the MM calculations with the ^{13}C-NMR chemical shifts of the steroidal skeletons. In this sense, the work of Wray [50] in 1981 had been inspirational. In his study on a small congeneric set of progestagens, Wray empirically investigated the effect of substituents on the ^{13}C-chemical shifts of the steroidal skeletons. He found a consistency in shifts for the same substituents. One year later, Schneider and Gschwendtner applied the same approach to larger data sets and their conclusion supported the usefulness of ^{13}C-NMR measurements in detecting small changes in geometries and electron densities in steroids.

Hoppen and Hammann [51] unsuccessfully tried to correlate the PR and AR binding affinities of a set of eight progestagen derivatives of norethisterone with their corresponding ^{13}C-NMR chemical shifts. This result is not surprising considering the limited amount of compounds analysed and the empirical approach followed.

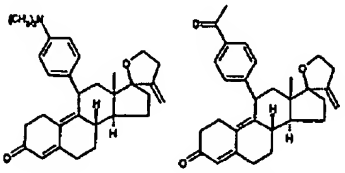
Despite the pioneering work of Hall and Sanders in 1980 [52], who published the first conformational ^{1}H-NMR study on steroids, at this point in time the relatively simple interpretability of ^{13}C-NMR shifts was preferred to the more complex ^{1}H-NMR shifts in SAR studies.

2.5. PR receptor mapping

The ultimate objective of every (Q)SAR study is not only limited to the identification of correlations between structure and activity, but it is also extended to the mapping of the active site of the studied target. A significant impact on these studies was provided by the discovery of progesterone antagonists. Unlike antagonists for, e.g., the oestrogen and androgen receptors, antagonists for the progesterone receptor have remained unknown for a very long time. It was only in 1982 that Roussel Uclaf reported the first high affinity antagonists. The prototype for this class of compounds is RU 486 or mifepristone (**19**), which, however, is also a very potent glucocorticoid antagonist. Since the mixed profile of RU 486 was considered a drawback for certain therapeutic applications, much research was devoted to find more selective anti-progestagens. Some examples are **20–23** [53, 54].



19 **20** **21**



22 **23**

First attempts to map the progesterone receptor were performed by Doré [55], Ojasoo [56] and Zeelen [57] in the late eighties. Doré performed a correspondence analysis on the selectivity of a set of steroids with respect to four different nuclear receptors (AR, PR, ER and GR). By projection of the principal components, receptor maps were obtained. In Ojasoo's study, the authors tried to map the PR and AR receptors by looking at the crystal structures of chemically different progestins and androgens and at their corresponding receptors. They came to the conclusion that space is present in both receptors around the 3-keto, 11β, 7α and, in PR, C21 positions. Hydrophobic pockets are distributed around them all. At the time that this paper was written, several receptors (ER, GR and PR) were cloned and sequenced. In Zeelen's receptor mapping study of PR it was concluded that a large hydrophobic pocket is present under the D ring and that possible structural modifications of the steroidal skeleton should take place under the D ring.

3. From the late 1980s till now

In the 1980s, major advances were made in characterizing the progesterone receptor, the biological target for progestagens. Modern biotechnology enabled the cDNA cloning of all steroid hormone receptors, including the progesterone receptor. The human progesterone receptor was found to occur in two forms, the full-length receptor, PR B, consists of 933 amino acids, while the truncated version, PR A, consists of 769 amino acids [58]. From then on the knowledge of steroid hormone action on a molecular level has dramatically increased [59]. Receptor cloning has also been of particular importance to the discovery and design of new progestagens. In the first place cell constructs have been prepared which contain both the progesterone receptor and a suitable reporter gene coupled to a promoter which is responsive to the progesterone receptor/agonist complex. The so-called transactivation assays, based on these constructs, lend themselves for rapid screening of large numbers of compounds, including non-steroids. In the second place it became possible to prepare pure receptor protein in relatively large amounts, which made it possible, at least in principle, to determine the three-dimensional structure via X-ray crystallography, high field NMR, etc. While the size of the complete receptor thus far has resisted such an approach, the hormone-binding domain of the progesterone receptor has been crystallized in the presence of progesterone as the ligand, and the structure determined by X-ray crystallography [60].

In the SAR field, the Comparative Molecular Field Analysis (CoMFA) method [61] undoubtedly represents a milestone in the development of three-dimensional-QSAR methods. Cramer first published it in 1988 and since then it has become of wide-spread use amongst medicinal chemists. As introduced in 1988, however, CoMFA (although powerful and elegant) needed several technical/statistical improvements, and because of its intrinsic requirement for molecular superposition, it determined one way of performing 3-D-QSAR studies, i.e. with alignment. It is not surprising that from 1988 till now many QSAR developments have been devoted either to improve CoMFA or to derive CoMFA-like approaches, or to develop 3-D-QSAR methods which, in contrast to CoMFA, would not require a molecular alignment.

Further, the 1990s were also characterized by the development of several receptor mapping techniques, spanning a wide range of complexity (from simple, CoMFA, to sophisticated, PARM).

3.1. 3-D-QSAR with alignment

In CoMFA, activities are predicted in terms of differences in steric and electrostatic interaction energies (molecular fields) between an atom probe and every atom in a molecule and every molecule in the data set. The interaction energies are calculated on a three-dimensional grid, whose points are set to an arbitrary distance within the CoMFA box. Compounds are by default centred in this box and superimposed on each other. Once the 3-D molecular fields are calculated for all molecules and accurate activities (mostly binding affinities or potencies) are available, the multivariate linear regression technique partial least square is used to derive a statistical model.

The statistical results can be further visualized back on the 3-D grid in terms of steric and electrostatic contours, which suggest where compounds should be modified in steric and electrostatic terms to enhance or decrease their activities. Because of this, CoMFA finally had become the tool that medicinal chemists had been waiting for for a long time. As introduced in 1988, however, the method suffered from several limitations such as a grid-dependence of the statistical results (absence of rotational and translational invariance), a very stiff Lennard-Jones potential for calculating steric interactions, and a partial charge type dependence of the electrostatic interactions [62]. Further CoMFA contours are not transferable because they are entirely dependent on the data set investigated.

Some of these limitations were successfully dealt with by the work of Baroni [63] to improve variable selection in partial least squares analyses, the work of Klebe [64] to improve the calculations of the electrostatic and steric interactions by Gaussian smoothing of the Lennard-Jones and Coulomb potentials and the work of Cho [65] to ensure the rotational and translational invariance of the statistical quantities.

The steroid data set on which CoMFA was first published became quickly known as the 'CoMFA data set'. Many new methods were subsequently tested on this data set to compare performances. The work of Oprea [66] is an interesting example, where he compared the minimal steric difference [67] approach with CoMFA. The results were not conclusive, but CoMFA was criticized for the too repulsive cut-off and for the stiffness of the Lennard-Jones potential. In 1994, Jain [68] published Compass, a method in which steric and electrostatic interactions are sampled close to the surface of compounds by means of neural networks. Its performance was tested on the steroid benchmark against CoMFA and the similarity index approach. Compass performed better.

The intrinsic requirement of an alignment and the need of finding the 'active' conformation were, however, criticized.

In 1996, Kellogg et al. [69] introduced the E and HE topological fields in 3-D-QSAR. In a CoMFA-like approach they substituted the scoring function used in CoMFA with the calculated E and HE fields. Their results showed that these fields perform better than the steric and electrostatic molecular fields. However, alignment is always needed and the interpretation of the E and HE contours is less intuitive than the corresponding contours in CoMFA.

3.2. 3-D-QSAR without alignment

Molecular superposition requires knowledge of the binding mode of a ligand towards its target. Unfortunately, this mode is not always known. In this case a theoretical superposition must be derived. This process is not always straightforward and objective, which suggests that analyses and corresponding conclusions based on theoretical alignments should be performed with great care. Developing a 3-D-QSAR method that is independent from molecular superposition is undoubtedly one of the greatest challenges in the field of QSAR. Several attempts have already been performed. In 1996, Silverman and Platt [70] published the Comparative Molecular Moment Analysis (CoMMA), where moments of inertia, dipole and quadruple moments are used as molecular descriptors. The statistical results compared favourably with CoMFA. Visualization of the results was not considered.

In 1997, simulated infrared spectra were used by Ferguson [71] in the EVA approach to predict binding affinities. EVA correlations compared well with CoMFA.

In the same year, Bravi [72] published the MS-WHIM (Molecular Surface-Weighted Holistic Invariant Molecular) indices. The WHIM indices had already been introduced earlier [73]. In the original WHIM work, the Cartesian coordinates of the nuclei were used to calculate roto-translational invariant molecular moments. In the extended MS approach, the same indices were calculated from Connolly molecular surface points. The approach was tested on the steroid benchmark and compared with CoMFA, Compass and the Carbo similarity indices. The results were more than favourable. Within this approach, however, visualization of the statistical results remains a critical issue.

Full exploitation of molecular spectra in QSAR studies was only recently published by Bursi [74], after almost 20 years the work of Wray on ^{13}C-NMR spectra in SAR studies. In the novel Comparative Spectra Analysis (CoSA) approach, experimental ^{1}H-NMR, mass, and IR spectra and simulated ^{13}C-NMR and IR spectra were used alone or in combination to predict the binding affinities of a set of progestagens. The results compared more than favourably with CoMFA, strongly supporting the use of spectroscopic fields in QSAR studies.

3.3. QSAR without 3-D

Although dominated by CoMFA, in the nineties QSAR studies continued to be performed by means of a great variety of methods.

One example is the work of Good [75] who implemented the Carbo index in a large variety of ways, and by means of the corresponding similarity matrices predicted the biological affinities of different data sets. The program GOLPE [63] was used as variable selector. The conclusion of this study was that similarity matrices should be more often used in QSAR studies.

A data set of progestagens was also investigated by means of a combination of genetic algorithm (GA) and neural networks (NN) [76]. In this study molecular descriptors were selected by means of GA and correlations with the binding affinities were obtained by means of NN. Conclusions were that a non-linear technique leads to better results on this data set than partial least squares or other linear regression techniques. The interpretability of the results, however, remained very difficult.

Novak [77] has recently published a study in which he presented several UV spectra for steroids of great interest, such as progesterone and testosterone. Assignment of the UV transitions were performed by means of AM1 MO calculations. Ionization potentials were further determined and a SAR study was attempted where ionization energies were correlated with receptor binding affinities. Unfortunately, no proper SAR could be derived on the basis of the available data.

3.4. Receptor mapping

In the 1990s many different approaches were developed to map the active sites of drug targets from a data set of ligands. These approaches were mostly applied to targets whose crystal structures were still unknown. Crystallization of the progesterone (PR) nuclear receptor and of some other nuclear receptors was achieved only recently [60]. The mapping of the progesterone receptor ligand-binding domain was therefore highly desirable.

One of CoMFA's great advantages is the visualization of the statistical results in terms of contours around the molecules. When binding data are considered for biological activity, these contours can also be seen as fingerprints

of the target's active site. In this sense, CoMFA belongs as well to receptor mapping approaches. Many CoMFA studies were therefore performed on PR alone or on PR and other nuclear receptors to obtain ideas on its active site or ideas on the differences between different active sites. Unfortunately, as published most of these studies were poor.

Another interesting receptor site model is Doweyko's Hypothetical Active Lactice (HASL) approach [78], where a four-dimensional lattice is build around each molecule in the data set. The four dimensions are based on the three Cartesian coordinates of the atoms and a fourth dimension, which can be a physical-chemical property of choice. The multidimensional lattices, which are generated, are used to compare molecules with each other and to generate QSARs. The results discussed in this study were encouraging.

In 1995, Hahn published a specific type of receptor site model, i.e., the Receptor Surface Model (RSM) [79]. Based on the idea of the active analogue approach, a dataset of active compounds is used to build the surface of the active site. Subsequently, 3-D energetics descriptors can be calculated from the interactions between RSM and ligand and used in the corresponding QSAR. A different selection of active compounds will obviously lead to a new RSM and, therefore, to new descriptors. Genetic algorithm is then used to select which descriptors (and therefore RSM models) are mostly valuable for the QSAR study considered. The approach was compared with CoMFA and Compass on different data sets. On the 'CoMFA data set' RSM does not perform better than the other approaches.

In 1998, the Pseudo Atomic Receptor Model (PARM) [80, 81] was published. PARM is, in fact, an improvement of Walter's Genetic Evolved Receptor Model (GERM) [82]. As in the other approaches, PARM needs a molecular alignment as well. Around the surface of each molecule a grid of points is built. At each grid point interaction energies are calculated between a given atom type and the closest atom in the molecule. Fifteen atom types are considered amongst which no atom at all is also considered. All possible combinations of atom types on the grid of points are considered, which leads to several models. At this point, in GERM, genetic algorithm evolves the individual combinations to the best combinations that are valuable for QSARs. In PARM the process is guided by a charge-dependent evolution of the individuals, where complementary charges between ligand and receptor are assumed. Partial charges are assigned to the atom types and only individuals or combinations of them, which are complementary to the partial charges in the molecules or molecule model, further evolve. PARM was tested amongst others on a steroid data set and compared with CoMFA. The cross-validated results as well as the predictive ability of the method were satisfactory.

4. Conclusions

Progestagens are steroid hormones which can be used in several therapeutic areas such as contraception, hormone replacement therapy and gynaecological disorders.

From the start they represented a very interesting class of compounds because of their relative rigidity and chemical diversity. As soon as reasonable amounts of progestagens were synthesized, they became objects of a great variety of studies, not only for synthetic and computational medicinal chemists, but also for computational chemists in general, crystallographers, and statisticians.

It is therefore not surprising that while historically looking at the origin and further developments of progestagens, we ended up looking to a large extent at the historical development of the (Q)SAR field.

It is undoubtedly true that we have come a long way in the process of understanding the properties and mechanisms of action of this class of compounds. Nowadays we can develop very potent and selective steroidal and non-steroidal progestagens, we can visualize the active site of the ligand-binding domain of the PR receptor and progesterone bound to it and we can derive reliable and robust QSAR models using a great variety of molecular descriptors from field to spectral descriptors.

The challenge is, however, not over. Genomics and chip technologies drive nowadays the search for new targets, combinatorial chemistry (CC) and high-throughput screening (HTS) dominate the lead discovery process, and high-speed synthesis (HSS) and early ADME (Adsorption Distribution Metabolism Excretion) accelerate the lead optimization cycles. Despite all this, independently from the level of sophistication at which we are operating, we are continuously confronting ourselves with the concept of correlating structures with activities whenever we need to come to a full understanding of a given molecular mechanism. In this sense alone, the knowledge and the experience that have been acquired in more than sixty years of (Q)SAR developments should be treasured.

References

[1] Inhoffen H.H., Logemann W., Hohlweg W., Serini A., Chem. Ber. 71 (1938) 1024–1030.

[2] Djerassi C., Miramontes L., Rosenkranz G., Sondheimer F., J. Am. Chem. Soc. 76 (1954) 4092–4094.

[3] Smith H., Hughes G.A., Douglas G.H., et al., J. Chem. Soc. (1964) 4472–4492.

[4] Junkmann K., Arch. Exp. Pathol. Pharmakol. 223 (1954) 244–253.

[5] Babcock J.C., Gutsell E.S., Herr M.E., Hogg J.A., Stucki J.C., Barnes L.E., Dulin W.E., J. Am. Chem. Soc. 80 (1956) 2904–2905.

[6] Ringold H.J., Perez Ruelas J., Batres E., Djerassi C., J. Am. Chem. Soc. 81 (1957) 3712–3716.

[7] Brückner K., Hampel B., Johnsen U., Chem. Ber. 94 (1961) 1225–1240.

[8] Laurent H., Schulz G., Wiechert R., Chem. Ber. 102 (1969) 2570–2582.

[9] Westerhof P., Reerink E.H., Recl. Trav. Chim. Pays-Bas 79 (1960) 771–783.

[10] Fried J., Sabo E.F., Grabowich P., Lerner L.J., Kessler W.B., Brennan D.M., Borman A., Chem. Ind. (London) (1961) 465–466.

[11] Van der Sijde D., Kooreman H.J., Jaitly K.D., Marx A.F., J. Med. Chem. 15 (1972) 909–914.

[12] De Winter M.S., Siegmann C.M., Szpilfogel S.A., Chem. Ind. (London) (1959) 905.

[13] Neumann F., Handbuch der Experimentellen Pharmacologie, Band XXII/1, Springer Verlag, 1968.

[14] McGuire J.L., Bariso C.D., Shroff A.P., Biochemistry 13 (1974) 319–322.

[15] Smith H.E., Smith R.G., Toft D.O., Neergaard J.R., Burrows E.P., O'Malley B.W., J. Biol. Chem. 249 (1974) 5924–5932.

[16] Kontula K., Janne O., Vihko R., de Jager E., de Visser J., Zeelen F.J., Acta Endocrinologica 78 (1975) 574–592.

[17] Raynaud J.P., Ojasoo T., Bouton M.M., Philibert D., Receptor Binding as a Tool in the Development of New Bioactive Steroids, in: Ariens J. (Ed.), Drug Design, vol. VIII, Academic Press, 1979.

[18] Raynaud J.P., Bouton M.M., Moguilewsky M., Ojasoo T., Philibert D., Beck, Labrie F., Mornon J.P., J. Steroid Biochem. 12 (1980) 143–157.

[19] Bergink E.W., Hamburger A.D., de Jager E., van der Vies J., J. Steroid Biochem. 14 (1981) 157–183.

[20] Bergink E.W., van Meel F., Turpijn E.W., van der Vies J., J. Steroid Biochem. 19 (1983) 1563–1570.

[21] Seeley D.H., Wang W.-Y., Salhanick H.A., J. Biol. Chem. 257 (1982) 13359–13366.

[22] Neelima, Seth M., Bhaduri P., Arzneim.-Forsch. (1986) 151–188.

[23] Hammett L.P., Chem. Rev. 17 (1935) 125–136.

[24] Hansch C., Fujita T., J. Am. Chem. Soc. 86 (1964) 1616–1626.

[25] Free S.M., Wilson J.W., J. Med. Chem. 7 (1964) 395–399.

[26] Teutsch G., Weber L., Page G., Shapiro E.L., Herzog H.L., J. Med. Chem. 16 (1973) 1370–1376.

[27] Wolff M.E., Hansch C., J. Med. Chem. 17 (1974) 898–899.

[28] Topliss J.G., Shapiro E.L., J. Med. Chem. 18 (1975) 621–623.

[29] Wolff M.E., Hansch C., Giannini D.D., Kollman P.A., Duax W.L., Baxter C.C., J. Steroid Biochem. 6 (1975) 211–214.

[30] Coburn R.A., Solo A.J., J. Med. Chem. 19 (1976) 748–754.

[31] Lee D.L., Kollman P.A., Marsh F.J., Wolff M.E., J. Med. Chem. 20 (1977) 1139–1146.

[32] Moriguchi I., Komatsu K., Matsushita Y., Anal. Chim. Acta 133 (1981) 625–636.

[33] Altona C., Geise H.J., Romers C., Tetrahedron 23 (1967) 439–463.

[34] Altona C., Geise H.J., Romers C., Tetrahedron 24 (1968) 13–32.

[35] Duax W.L., J. Steroid Biochem. 15 (1981) 41–47.

[36] Duax W.L., J. Tox. Envir. Hlth. 4 (1978) 205–227.

[37] Duax W.L., Griffin J.F., Rohrer D.C., X-Ray Crystallography and Drug Action, in: Horn A.S., de Router C.J. (Eds.), Course Int. Sch. Crystallogr. 9th, Oxford University Press, Oxford, 1984, pp. 405–426.

[38] Duax W.L., Griffin J.F., Rohrer D.C., in: Zalewski R.I., Skolik J.J. (Eds.), Natural Products Chemistry, 1984, pp. 3985–3996.

[39] Van der Broek A.J., Broess A.I.A., Heuvel M.J., de Jongh H.P., Zeelen F.J., Steroids 30 (1977) 481–510.

[40] Zeelen F.J., Biol. Act. Chem. Struct. (1977) 147–159.

[41] Bohl M., Kaufmann G., Hubner M., Reck G., Kretschmer R.-G., J. Steroid Biochem. 23 (1985) 895–900.

[42] Bohl M., Simon Z., Vlad A., Kaufmann G., Ponsold K., Z. Naturforsch. 42c (1987) 935–940.

[43] Broess A.I.A., Groen M.B., Hamersma H., Bioorg. Med. Chem. Lett. 7 (1997) 2925–2928.

[44] Broess A.I.A., Groen M.B., Hamersma H., Bioorg. Med. Chem. Lett. 7 (1997) 2929–2934.

[45] Van der Broek A.J., Broess A.I.A., Heuvel v.d. M.J., Jongh de H.P., Leemhuis J., Schönemann K.H., Smits J., Visser de J.N., Vliet van P., Zeelen F.J., Steroids 30 (1977) 481–510.

[46] Allinger N.J., Lane G.A., J. Am. Chem. Soc. 96 (1974) 2937–2941.

[47] Schneider H.-J., Gschwendtner W., Weigand E.F., J. Am. Chem. Soc. 101 (1979) 7195–7198.

[48] Schneider H.-J., Buchheit U., Gschwendtner W., Lonsdorfer M., Mol. Struct. Biol. Act. (1982) 165–179.

[49] Schneider H.-J., Gschwendtner W., J. Org. Chem. 47 (1982) 4216–4221.

[50] Wray V., Tetrahedron 37 (1981) 777–780.

[51] Hoppen H.-O., Hammann P., Acta Endocrinol. 115 (1987) 406–412.

[52] Hall L.D., Sanders J.K.M., J. Am. Chem. Soc. 102 (1980) 5703–5711.

[53] Teutsch G., Philibert D., Progesterone Antagonists in Reproductive Medicine and Oncology, Human Reproduction, vol. 9 Suppl. 1, Oxford University Press, Oxford, 1994, pp. 12–32.

[54] Schoonen W.G.E.J., Vermeulen G.J., Deckers G.H., Verbost P.M., Kloosterboer H.J., Curr. Top. Steroid Res. 2 (1999) 15–54.

[55] Doré J.-C., Gilbert J., Ojasoo T., Raynaud J.-P., J. Med. Chem. 29 (1986) 54–60.

[56] Ojasoo T., Delettré J., Mornon J.P., Turpin-VanDycke C., Raynaud J.P.J., Steroid Biochem. 27 (1987) 255–269.

[57] Groen M.B., van der Heuvel M.J., Deckers G.H.J., Kloosterboer H.J., Kelder J., Zeelen F.J., Organon Internal Communication, 1988.

[58] Misrahi M., Atger M., d'Auriol L., Loosfelt H., Meriel C., Fridlansky F., et al., Biochem. Biophys. Res. Commun. 143 (1987) 740–748.

[59] Beato M., Cell 35 (1998) 335–344.

[60] Williams S.P., Sigler P.B., Nature 393 (1998) 392–395.

[61] Cramer R.D., Patterson D.E., Bunce J.D., J. Am. Chem. Soc. 110 (1988) 5959–5967.

[62] Bursi R., Grootenhuis P.D.J., J. Comput.-Aided Mol. Des. 13 (1999) 221–232.

[63] Baroni M., Constantino G., Cruciani G., Riganelli D., Valigi R., Clementi S., Quant. Struct.-Act. Relat. 12 (1993) 9–20.

[64] Klebe G., Abraham U., Mietzner T., J. Med. Chem. 37 (1994) 4130–4146.

[65] Cho S.J., Tropsha A., J. Med. Chem. 38 (1995) 1060–1066.

[66] Oprea T.I., Ciubotariu D., Sulea T.I., Simon Z., Quant. Struct.-Act. Relat. 12 (1993) 21–26.

[67] Simon Z., Rev. Roumaine Chimie 37 (1992) 323–327.

[68] Jain N., Koile K., Chapman D., J. Med. Chem. 37 (1994) 2315–2327.
[69] Kellogg G.E., Kier L.B., Gaillard P., Hall L.H., J. Comput.-Aided Mol. Des. 10 (1996) 513–520.
[70] Silverman B.D., Platt D., J. Med. Chem. 39 (1996) 2129–2140.
[71] Ferguson A.M., Heritage T., Jonathon P., Pack S.E., Phillips L., Rogan J., Snaith P.J., J. Comput.-Aided Mol. Des. 11 (1997) 409–422.
[72] Bravi G., Gancia E., Mascagni P., Pegna M., Todeschini R., Zaliani A., J. Comput.-Aided Mol. Des. 11 (1997) 79–92.
[73] Todeschini R., Lasagni M., Marengo E., J. Chemom. 8 (1994) 263–272.
[74] Bursi R., Dao T., van Wijk T., de Gooyer M., Kellenbach E., Verwer P., J. Chem. Inf. Comp. Sci. 39 (1999) 861–867.
[75] Good C., Peterson S.J., Richards W.G., J. Med. Chem. 36 (1993) 2929–2937.
[76] Van Helden S., Hamersma H., van Geerestein V.J., Genetic Algorithms in Molecular Modelling, Academic Press, London, 1996, pp. 159–192.
[77] Novak I., Kovac B., Biophys. Chem. 78 (1999) 233–240.
[78] Doweyko A.M., J. Med. Chem. 31 (1998) 1396–1406.
[79] Hahn M., Rogers D., J. Med. Chem. 38 (1995) 2091–2102.
[80] Chen H., Zhou J., Xie G., J. Chem. Inf. Comput. Sci. 38 (1998) 243–250.
[81] Santagati M., Chen H.M., Santagati A., Modica M., Guccione S., Uccello Barretta G., Balzano F., in: Gundertofte K., Jorgensen F.S. (Eds.), Molecular Modelling and Prediction of Bioactivity, Kluwer Academic/Plenum Publishers, New York, 2000, pp. 443–450.
[82] Walters D.E., Hinds R.M., J. Med. Chem. 37 (1994) 2527–2531.